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INVENTOR(s)/APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
Martin	**Pierre**		**Rheinfelden, Switzerland**
Berens	**Ulrich**		**Binzen, Germany**
Boudier	**Andreas**		**Basel, Switzerland**
Dosenbach	**Oliver**		**Bamlach, Germany**

TITLE OF THE INVENTION (280 characters max)

Synthesis Methods and Intermediates for the Manufacture of Rizatriptan

CORRESPONDENCE ADDRESS

JoAnn Villamizar
Ciba Specialty Chemicals Corporation
Patent Department

Mailing Address	State	Zip Code	Country
540 White Plains Road P.O. Box 2005 Tarrytown	NEW YORK	10591-9005	U.S.A.

ENCLOSED APPLICATION PARTS *(check all that apply)*

- ☑ **48** pages of Specification (and any claims)
- ☑ **1** pages of Abstract
- ☐ ___ sheets of Drawing(s)
- ☐ Other (specify)

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Respectfully submitted,

Tyler A. Stevenson
Agent for Applicants
Reg. No. 46,388

Tel. No. (914) 785-7127
Date: February 10, 2004

Synthesis Methods and Int rmediates for the Manufacture of Rizatriptan

Summary of the invention

The present invention provides a novel process (= method) for the manufacture of tryptamine derivatives such as Rizatryptan, as well as novel intermediates for said synthesis and novel process steps for their synthesis. Rizatriptan and the related derivatives are known to be pharmaceutically useful, e.g. in the treatment of migraine.

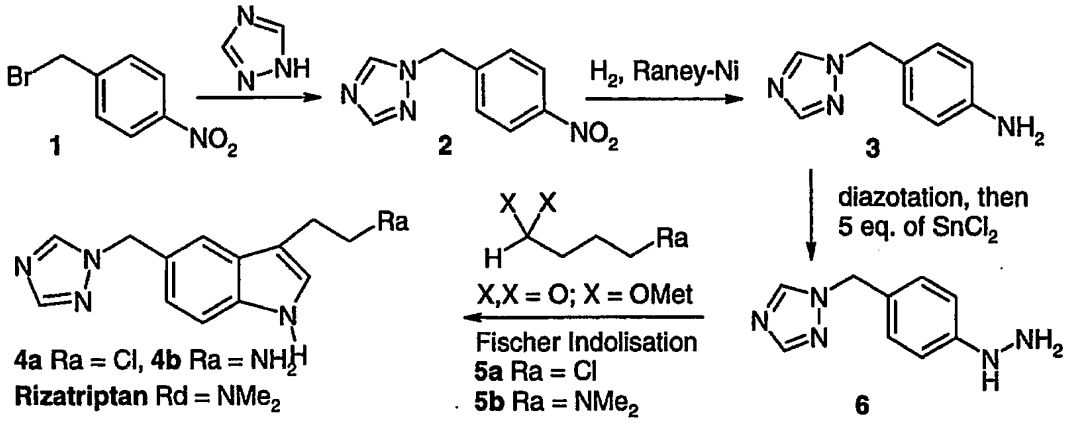
Background of the Invention

A number of ways are known for the synthesis of Rizatriptan (= 3-[2-(dimethylamino)ethyl]-5-(1,2,4-triazol-1-ylmethyl)indole), and salts thereof, such as the benzoate. Rizatriptan is useful in the treatment of migraine. One known way (see EP 0 497 512 A2) for the synthesis is as follows: Alkylation of 1,2,4-triazol with 4-nitrobenzylchloride **1** leads to a mixture of two products resulting from alkylation of either the 1- or the 4-position of the triazole. The undesired 4-alkylation product can be removed (see *Tetrahedron Lett.* **1994**, *35*, 6981) or its formation can be avoided by alkylation of 4-amino-1,2,4-triazol and the subsequent removal of the 4-amino group by diazotation (see EP 0 573 221). Catalytic hydrogenation of the nitro group of **2** yields aniline **3** in quantitative amounts. Still it would be desirable to avoid the formation of the undesired 4-alkylation product, which is one of the problems to be solved by the present invention.

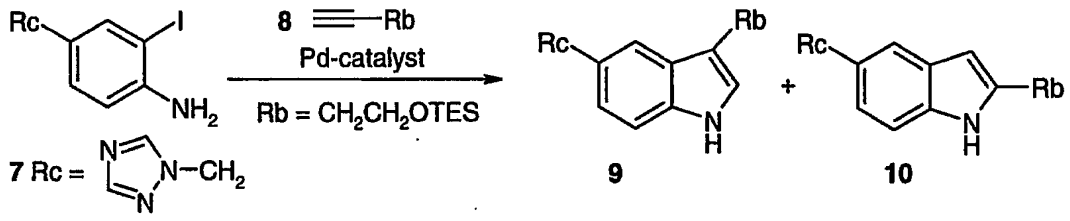
Diazotation of **3** and reduction of the diazonium salt with excess tin(II)chloride results in the phenyl hydrazone **6** (see *J. Med. Chem.* **1995**, *38*, 1799). However, tin salts are of low acceptability especially for pharmaceuticals, and in the form of sodium sulphite a more acceptable reducing agent was identified (see EP 0 573 221 A1).

The reaction of **6** or a salt of it under acidic conditions with aldehyde **5a** or an acetal thereof produces, depending on the detailed reaction conditions, the tryptamine derivatives **4a** or **4b**, while with aldehyde **5b** or an acetal thereof Rizatriptan is directly obtained. Using **5b** is preferable, as in this case Rizatriptan is obtained directly, though the synthesis via the dimethyl acetal of **5b** requires additional steps (see *J. Org. Chem.* **1994**, *59*, 3738), whereas alkylation of dimethyl-amine with **4a** or the reductive methylation of **4b** give Rizatriptan only in relatively low yields.

The conversion of **3** into **6** and the subsequent Fischer-Indolisation with **5b** may also be combined into a one-pot procedure (see EP 0 573 221 A1) to produce, after chromatography, Rizatriptan in 45% yield.



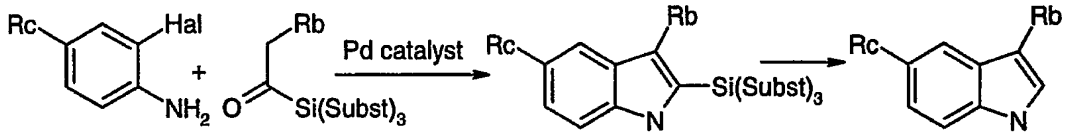
The low yields in the indole forming reaction have been attributed to "triazol polymerization", the avoidance of which is another problem to be solved by the present invention, and led to other approaches (see WO 95/32197). There, a 2-iodo aniline such as **7**, which is obtained via iodination of **3**, is reacted with an alkyne **8** (with TES representing triethylsilyl) in the presence of a homogenous Pd-catalyst to give a mixture of the protected tryptopholes **9** and **10**. These can be separated without a need for chromatography, and after deprotection of **9** the corresponding tryptophol can be transformed into Rizatriptan in 73% yield.



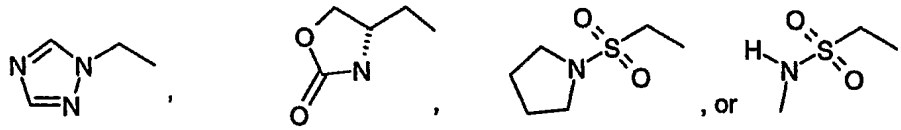
Although no additives such as triphenyl phosphine are required, a rather high loading of expensive homogenous palladium (e.g. 2 to 3 mol-%) is required to convert **7** into **9** and **10**. Avoidance of the use of such a high palladium amount is another problem to be solved by the present invention.

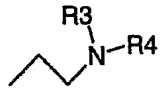
Another approach to overcome the problems due to "triazole polymerisation" utilizes the Pd-catalysed coupling of a 2-halo or 2-trifluormethansulfonyl substituted aniline with an acyl silane. After de-silylation of the obtained 2-silyl indole derivatives, tryptanes such as

Rizatriptan can be obtained (US 5,808,064) (as well as Zolmitriptan, Almitriptan or Sumatriptan). Though this procedure is efficient, it suffers from the fact that acyl silanes are not readily available and still soluble (homogenous) palladium catalysts in high amount (e.g. 2 to 3 mol-%) are required. One of the problems to be solved by the present invention is to avoid the acyl silanes and the homogenous palladium catalysts.



Hal = Br, I or OSO_2CF_3

Rc = 

Rb = 

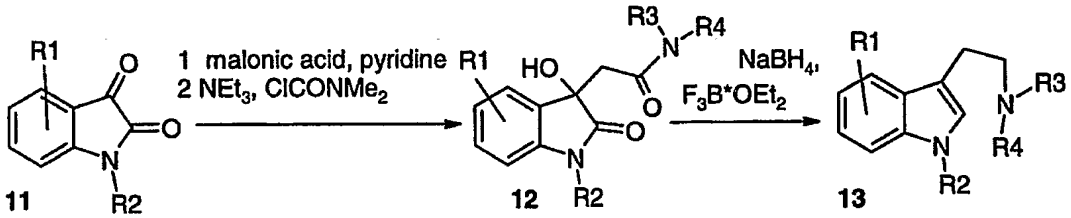
, R3, R4 = H, lower alkyl (e.g. methyl)

Subst = C_{1-6}alkyl, OC_{1-6}alkyl, phenyl

The present invention presents a solution for the preparation of Rizatriptan, which avoids the disadvantages mentioned above associated with the Fischer indolisation procedure and also avoids the use of homogeneous palladium catalysts, thus especially solving the above-mentioned problems and offering further synthesis advantages.

General description of the invention

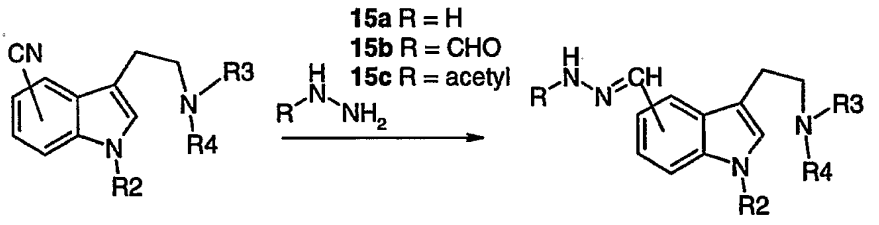
A surprisingly simple approach to tryptophanes has been identified by converting a substituted isatine such as **11** into an amide such as **12**, and the subsequent (optionally one-pot) reduction of the latter into the tryptamine **13** (see parallel patent application PCT/EP03/50992 which is incorporated by reference in its entirety, or especially in this regard)



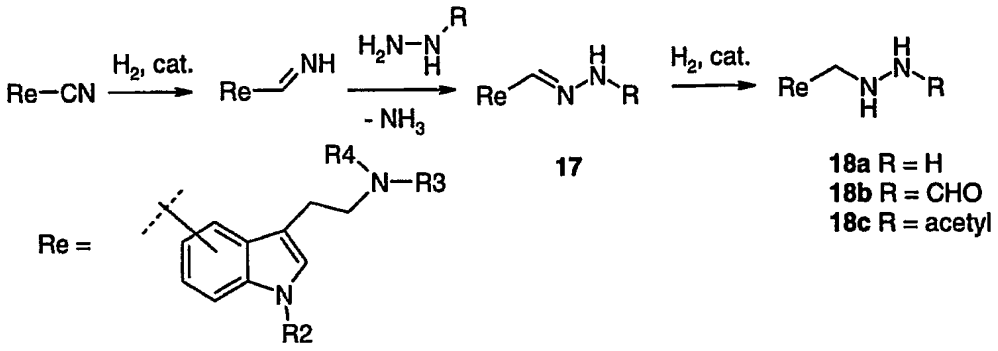
R1 is hydrogen or a substituent such as cyano or a group selected from halogen or an aryl ester of a substituted sulfonic acid, and R2, R3 and R4, where present, respectively, preferably have the meanings defined below.

Of particular interest are compounds where R1 is a cyano group, such as **14**, which is readily available by the methods described e.g. in US 5,510,359 or in Ciba Patent Application PCT/EP03/50992 (which is incorporated by reference especially in this regard).

It has now been found surprisingly that when a nitrile compound such as **14** is reacted under hydrogenation in the presence of hydrazine **15a** (R = H) or an R = acyl protected hydrazine such as N-formyl hydrazine **15b** or N-acetyl hydrazine **15c** the corresponding hydrazones **16a-c** or **18a-c** respectively are obtained, this reaction offering a new route for the synthesis of tryptamines:

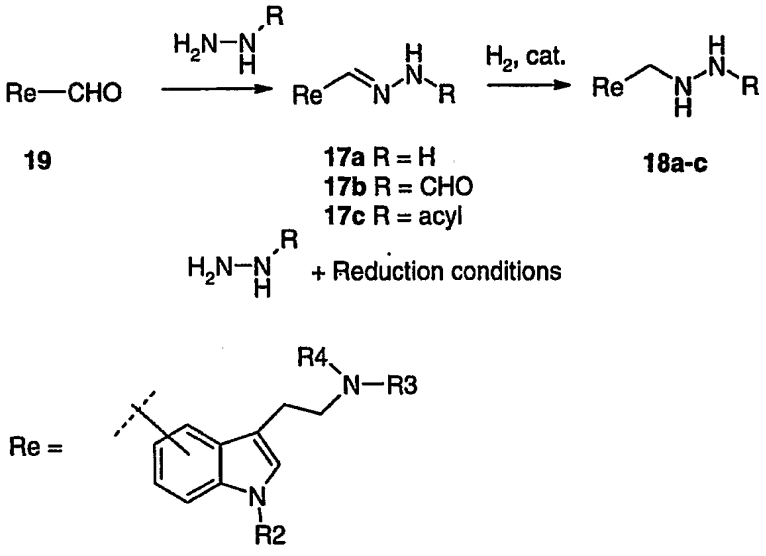


The whole conversion of a nitrile to the hydrazine via the hydrazone follows the general scheme below.



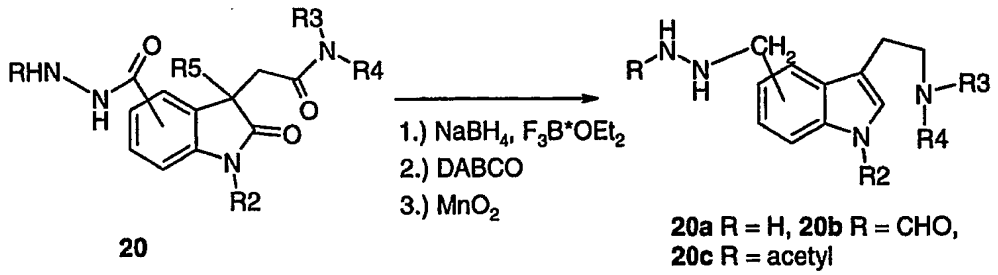
wherein R is hydrogen, formyl or acetyl or most generally acyl.

Alternatively, the hydrazones **17** or the hydrazines **18** can be obtained by reaction of aldehyde **19** (obtainable e.g. according to US 5,510,359 or according to Ciba Patent Application PCT/EP03/50992 which are herewith incorporated by reference preferably regarding this aspect) with the hydrazines **15a, 15b or 15c**, to give **17a-c**, followed by reduction to give **18a-c**.



(R is hydrogen, formyl or acetyl)

Further, carbonic acid hydrazides such as **20** can also be converted into a hydrazine such as 20a by means of said borane reduction protocol:



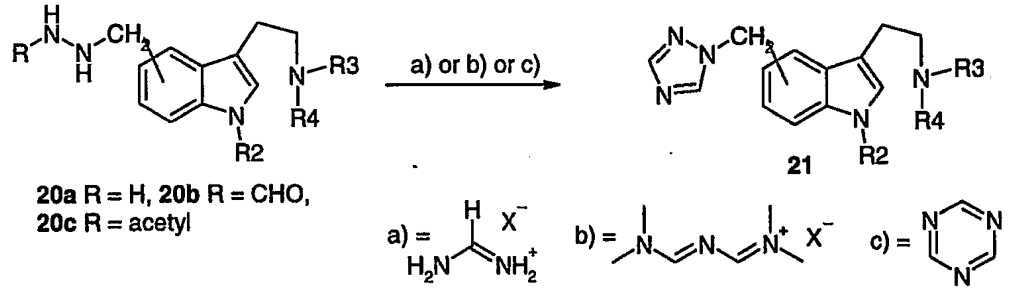
20

20a R = H, **20b** R = CHO,
20c R = acetyl

(R is hydrogen, R5 is hydrogen or preferably hydroxy)

These and related ways described in detail below allow for the synthesis of Hydrazines **20a, 20b or 20c.**

Hydrazines, such as **20a, 20b or 20c** can then, in the most general and most important aspect of the invention, be converted efficiently into 1-substituted 1,2,4-triazoles, especially by reacting them with either a formamidinium salt (acetate or chloride) (see e.g. *Chem. Ber.* **1981**, *114*, 2825), or with Gold's reagent (see e.g. *J. Med. Chem.* **1992**, *35*, 2392), or also with 1,3,5-triazine in a suitable solvent (see e.g. *J. Org. Chem.* **1956**, *21*, 1037), or in analogy to the methods described for different hydrazines in US 4,556,717.



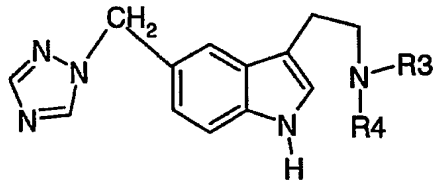
20a R = H, **20b** R = CHO,
20c R = acetyl

21

The final product, either obtained in free form or in salt form or after transformation of the free form into a salt or a salt into a different salt, is preferably Rizatriptan **21** (R2 =H, R3 = R4 = CH_3) or a salt thereof.

Detailed Description of the invention

The invention relates in a first embodiment to a process for the manufacture of an 1,2,4-triazol-1-yl compound of the formula [A],



[A]

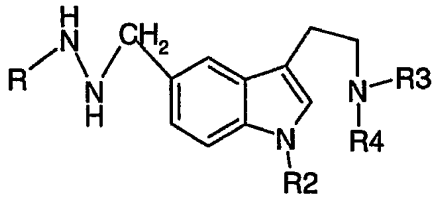
or a salt thereof,

wherein

each of R3 and R4 is hydrogen or preferably lower alkyl

said process comprising

reacting a hydrazine compound of the formula [B]



[B]

wherein

R is hydrogen or acyl

R2 is hydrogen or (less preferably) a protecting group, and

R3 and R4 have the meanings as defined above for compounds of the formula [A],

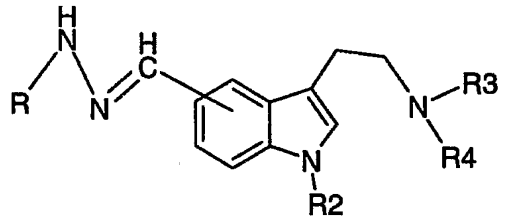
or a salt thereof with a 1,2,4-triazolyl forming reagent, where R is acyl in formula [B], preferably removing an acyl group R before the reaction of the compound of the formula [B] with the 1,2,4-triazolyl forming reagent e.g. by hydrolysis or catalytic hydrogenation,

if present removing any protecting group R2 to produce the free compound, or a salt, of a compound of the formula [A],

and, if desired, converting a salt of a resulting compound of the formula [A] into a free form of a compound of the formula [A], converting a resulting free form of a compound of the formula [A] into a (preferably pharmaceutically acceptable) salt or converting a salt of a compound of the formula [A] into a different (preferably pharmaceutically acceptable) salt.

Preferably, in the process described in the last paragraph, R in the compound of formula [B] is hydrogen and/or lower alkanoyl, especially acetyl or formyl, and/or acetyl, and lower alkanoyl, especially formyl or acetyl, is hydrolytically removed prior to the reaction with the formamidinium salts or derivatives, and in each of formulae [A] and [B] each of R3 and R4 is methyl and the compound of the formula [A] is produced in free form or in the form of a pharmaceutically acceptable salt.

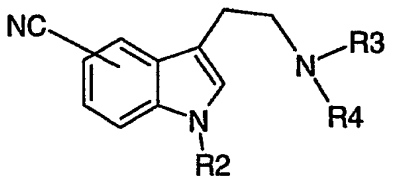
In a further embodiment, the invention relates to a process for the manufacture of a compound of the formula [B] as shown above, or a salt thereof, wherein R, R2, R3 and R4 have the meanings given in any one of the first or preferably the second of the preceding paragraphs, comprising reacting a compound of the formula [D],



[D]

wherein R, R2, R3 and R4 are as just defined, or a salt thereof, under reductive conditions to a compound of the formula [B], or a salt thereof;

The invention, in a further embodiment, also relates to a process for the manufacture of a compound of the formula [D] shown above, wherein R, R2, R3 and R4 are as defined in the first or preferably in the second of the preceding paragraphs, said process comprising reacting a compound of the formula [E],



[E]

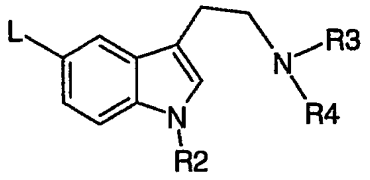
wherein each of R2, R3 and R4 is as just defined, or a salt thereof with a hydrazine of the formula [F],

$$R\text{-}NH\text{-}NH_2 \qquad [F]$$

wherein R is hydrogen or acyl, preferably hydrogen or lower alkanoyl (which is more preferably formyl or especially acetyl), or a salt thereof, under reductive conditions to a compound of the formula [D] as defined above, or a salt thereof.

The invention also relates to a compound of the formula [D] as shown above, wherein R, R2, R3 and R4 are as defined there, more preferably wherein R is hydrogen or acyl, R2 is hydrogen or a protecting group, preferably hydrogen, and each of R3 and R4 is hydrogen or preferably lower alkyl, more preferably methyl, in any one of claims 1 or preferably 2, or a salt thereof.

In yet another embodiment, the invention relates to a process for the manufacture of a compound of the formula [E] as shown above, wherein R2 is hydrogen or a protecting group, preferably hydrogen, and each of R3 and R4 is hydrogen or preferably lower alkyl, more preferably methyl, or a salt thereof, comprising reacting a compound of the formula [G],

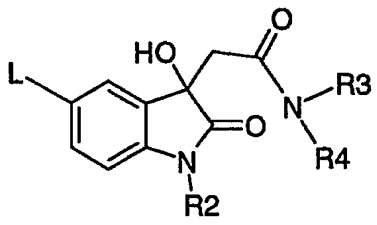


[G]

wherein R2, R3 and R4 are as just defined, or a salt thereof, and L is halogen, unsubstituted or substituted alkanesulfonyloxy or arylsulfonyloxy, with a cyanide salt (e.g. $Zn(CN)_2$ in the presence of a homogenous palladium catalyst; and alkali metal cyanide in the presence of a Ni(0) complex; or copper(I)cyanide) where required in the presence of a catalyst, to the compound of the formula [E] as defined above, or a salt thereof.

The invention also relates to a compound of the formula [G] as shown above, wherein each of R2, R3 and R4 is as defined in the last paragraph, or a salt thereof.

In still another embodiment, the invention relates to a process for the manufacture of a compound of the formula [G] as shown above, or a salt thereof, wherein L, R2, R3 and R4 are as defined in the last two paragraphs, comprising reducing a compound of the formula [H],

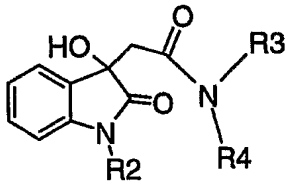


[H]

wherein L, R2, R3 and R4 are as defined in the last two paragraphs, , in the presence of borane, which is preferably obtained in situ from sodium boro hydride and a lewis acid, and subjecting the resulting product(s) to removal of borane from any amino borane intermediates and to a subsequent oxidation/de-hydrogenation with an oxidant, for example a quinone or preferably manganese dioxide, in order to yield a compound of the formula [G], or a salt thereof, as just defined;

where preferably the compound of the formula [H], is manufactured

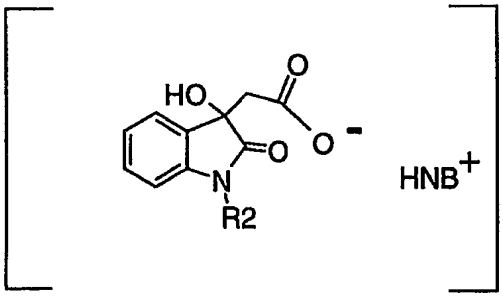
a) either from a compound of the formula [I],



[I]

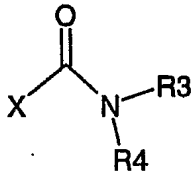
wherein R2 is a protecting group or preferably hydrogen, and each of R3 and R4 is hydrogen or preferably lower alkyl, more preferably methyl, by reacting it with an electrophile capable of introducing group L, especially halogen by reaction with a halo-succinimide, resulting in a corresponding compound of the formula [H],

where preferably the compound of the formula [I] as defined above, is formed by reacting a compound of the formula [K],



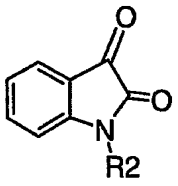
[K]

wherein R2 is a protecting group or preferably hydrogen and NB is a tertiary nitrogen base where the nitrogen is not part of a ring, with a compound of th formula [L],



[L]

wherein X is halogen and R3 and R4 are as defined in any one of claims 1 or preferably 2, to give the compound of the formula [K] as defined above;
where preferably the compound of the formula [K] is obtained by reacting an isatine compound of the formula [M],

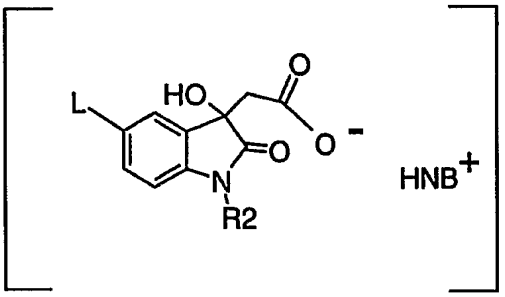


[M]

wherein R2 is a protecting group or preferably hydrogen, with malonic acid in the presence of a pyridine, especially pyridine and/or one or more picolines, in the absence or presence of a N,N-di-(lower alkyl)-lower alkanoylamide, a lower alkanol, e.g. methanol or ethanol, or a di-lower alkylsulfoxide, e.g. dimethylsulfoxide, especially N,N-dimethyl formamide, advantageously in the additional presence of an ester, preferably a lower alkyl alkanoate, more preferably ethyl acetate as a cosolvent, followed by conversion of the resulting compound which is present a a salt of a pyridine into the salt of the base NB given in formula [K], where preferably the reaction of the isatine compound of the formula [M] and the conversion of the product salt of a pyridine into the corresponding salt of the formula [K] and more preferably also the reaction of a compound of the formula [K] with a compound of the formula [L] to a compound of the formula [I] take place in the same reaction vessel;

or

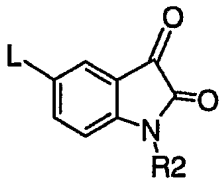
b) more preferably by reacting a compound of the formula [K*],



[K*]

wherein R2 is a protecting group or preferably hydrogen, L is a leaving group selected from halogen, unsubstituted or substituted alkanesulfonyloxy or arylsulfonyloxy, and NB is a tertiary nitrogen base where the nitrogen is not part of a ring, with a compound of the formula [L] shown under a), wherein X is halogen and R3 and R4 are as defined in any one of claims 1 or preferably 2, to give the compound of the formula [H] as defined above;

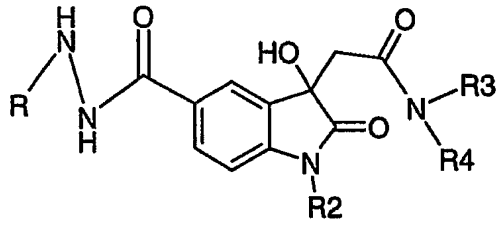
where preferably the compound of the formula [K*] is obtained by reacting an isatine compound of the formula [M*],



[M*]

wherein R2 has the meanings given in any one of claims 1 or preferably 2 and L is halogen, unsubstituted or substituted alkanesulfonyloxy or arylsulfonyloxy, with malonic acid in the presence of a pyridine, especially pyridine and/or one or more picolines in the absence or presence of a N,N-di-(lower alkyl)-lower alkanoylamide, a lower alkanol, e.g. methanol or ethanol, or a di-lower alkylsulfoxide, e.g. dimethylsulfoxide, especially N,N-dimethyl formamide, advantageously in the presence of an ester, preferably lower alkyl alkanoate, especially ethyl acetate as a cosolvent, followed by conversion of the resulting compound which is present a a salt of a pyridine into the salt of the base NB given in formula [K*], where the reaction of the isatine compound of the formula [M*] and the conversion of the product salt of a pyridine into the corresponding salt of the formula [K*] preferably take place in the same reaction vessel.

Yet another embodiment of the invention relates to a process for the manufacture of a compound of the formula [B] as shown above, wherein R is hydrogen, R2 is hydrogen or a protecting group, and each of R3 and R4 is hydrogen or lower alkyl, or a salt thereof, comprising reducing a compound of the formula [C],

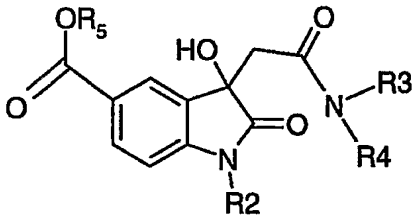


[C]

wherein R is hydrogen, R2 is a protecting group or preferably hydrogen and each of R3 and R4 is hydrogen or preferably lower alkyl, more preferably methyl, or a salt thereof, in the presence of borane, which is preferably obtained in situ from sodium boro hydride and a lewis acid, and subjecting the resulting product(s) to removal of borane from any amino borane intermediates and to a subsequent oxidation/de-hydrogenation with manganese dioxide, thus producing a compound of the formula [B] as just defined, or a salt thereof.

The invention also relates to a compound of the formula [C] as shown above, wherein R is acyl or preferably hydrogen, R2 is a protecting group or preferably hydrogen, and each of R3 and R4 is hydrogen or preferably lower alkyl, more preferably methyl, or a salt thereof.

A further embodiment of the invention relates to a process for the manufacture of a compound of the formula [C] as shown above, wherein R, R2, R3 and R4 are as defined in the last paragraph, or a salt thereof, comprising reacting a compound of the formula [N],



[N]

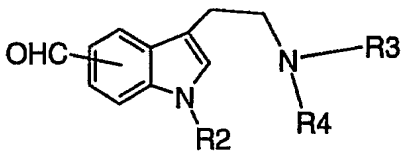
wherein R2, R3 and R4 are as just defined and R_5 is unsubstituted or substituted alkyl , preferably lower alkyl, more preferably methyl or ethyl, with a hydrazine of the formula [F]

$R\text{-}NH\text{-}NH_2$ [F]

wherein R is acyl, especially lower alkanoyl, such as acetyl or formyl, or most preferably hydrogen, or a salt thereof,
to a corresponding compound of the formula [C].

A further embodiment of the invention relates to a process for the manufacture of a compound of the formula [N] as shown above, wherein R2 is a protecting group or preferably hydrogen, and each of R3 and R4 is hydrogen or preferably lower alkyl, more preferably methyl, comprising reacting a compound of the formula [H] as shown above, wherein R2, R3 and R4 are as just defined, and L is halogen, unsubstituted or substituted alkanesulfonyloxy or arylsulfonyloxy, by reaction with carbon monoxide in the presence of the corresponding alcohol R_5-OH in the presence of a catalyst and a tertiary nitrogen base, to the compound of the formula [N] as just defined, where preferably the compound of the formula [H], is manufactured as described above.

A further embodiment of the invention relates to a process for the manufacture of a compound of the formula [B] as shown above wherein R is acyl, especially lower alkanoyl, more especially formyl or acetyl, or preferably hydrogen, R2 is a protecting group or preferably hydrogen, and each of R3 and R4 is hydrogen or preferably lower alkyl, more preferably methyl, or a salt thereof, comprising reacting an aldehyde of the formula [O],



[O]

wherein each of R2, R3 and R4 is as just defined, or a salt thereof, either under simultaneous reduction by way of reductive amination directly to a corresponding compound of the formula [B], or by first reacting with the hydrazine and then subsequent reduction of the resulting hydrazone of the formula [D] as shown above, wherein R, R2, R3 and R4 are as just defined, with a hydrazine of the formula [F] as shown above wherein R is as just defined for formula [B], or a salt thereof, to a compound of the formula [B] as defined above, or a salt thereof,
where the compound of the formula [O] given above, or a salt thereof, is preferably obtained from a compound of the formula [G] shown above, wherein each of R2, R3 and R4 is as just defined and L is halogen, especially iodo or bromo, or a salt thereof,

by reacting it with first a lithium alkyl compound to form the lithio derivative and then with DMF or triethyl formate, to obtain a corresponding compound of the formula [O], or a salt thereof after hydrolysis.

In an important aspect, the invention relates to a compound of the formula [B] as shown above, wherein R is acyl, preferably lower alkanoyl, such as formyl or acetyl, R2 is a protecting group or preferably hydrogen, and each of R3 and R4 is hydrogen or preferably lower alkyl, more preferably methyl, or a salt thereof.

Further embodiments of the invention relate to a compound of the formula [E] as shown above, wherein R2 is a protecting group and each of R3 and R4 is hydrogen or preferably lower alkyl, more preferably methyl, or a salt thereof; or to

a compound of the formula [H] as shown above, wherein R2 is a protecting group, L is halogen, unsubstituted or substituted alkanesulfonyloxy or arylsulfonyloxy and each of R3 and R4 is hydrogen or preferably lower alkyl, more preferably methyl, or a salt thereof

Unless otherwise indicated, the general terms and names used in the description of the present invention preferably have the following meanings (where more specific definitions, in each case separately, or in combination, may be used to replace more general terms in order to define more preferred embodiments of the invention):

Where compounds or a compound are mentioned, this means these compounds or salts thereof, e.g., where in the compounds acidic groups (e.g. carboxyl or sulfonyl) are present, salts with bases, such as alkali metal salts or ammonium salts, where basic groups (e.g. amino, imino, hydrazine) are present, acid addition salts, e.g. with inorganic acids, such chlorides or sulfates, or with organic acids, e.g. sulfonic or carbonic acids, such as methane sulfonates, benzoates or acetates, where appropriate and expedient. Where both acidic and basic groups are present, also internal salts may be formed. Salts of compounds of the formula [A] are preferably pharmaceutically acceptable salts, while for the purposes of isolation or purification especially of the salts of other compounds mentioned above and below it is also possible to use pharmaceutically unsuitable salts, for example picrates or perchlorates. Only the pharmaceutically acceptable salts or the free compounds (optionally in the form of pharmaceutically compositions) of the compounds of formula [A] are used therapeutically and they are therefore preferred.

The term "lower" defines a moiety with up to and including maximally 7, especially up to and including maximally 4, carbon atoms, said moiety being branched or straight-chained. Lower alkyl, for example, is methyl, ethyl, n-propyl, sec-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl or n-heptyl, or preferably methyl. Lower alkanoyl is preferably formyl or especially acetyl.

In "un-substituted or substituted", "substituted", wherever used for a moiety, means that one or more hydrogen atoms in the respective molecule, especially up to 5, more especially up to three, of the hydrogen atoms are replaced by the corresponding number of substituents which preferably are independently selected from the group consisting of alkyl, especially lower alkyl, for example methyl, ethyl or propyl, hydroxy, mercapto, nitro, cyano, halo, halo-lower alkyl, for example trifluoromethyl, C_6-C_{16}-aryl, especially phenyl or naphthyl (where C_6-C_{16}-aryl, especially phenyl or napthyl, is unsubstituted or substituted by one or more, especially up to three moieties selected from N,N-di-lower alkylamino, N-phenyl-lower alkylamino, N,N-bis(phenyl-lower alkyl)-amino, and halo-lower alkyl, e.g. trifluoromethyl), C_3-C_{10}-cycloalkyl, lower alkoxy, for example methoxy, aryl-lower alkoxy, e.g. phenyl-lower alkoxy, lower alkanoyloxy, N,N-di-lower alkylamino, N-phenyl-lower alkylamino, N,N-bis(phenyl-lower alkyl)-amino, di-lower alkylamino, unsubstituted or lower alkyl substituted and/or mono- or di-oxosubstituted heterocyclylenyl or heterocyclyl, e.g. unsubstituted or lower alkyl substituted-imidazolidin-2,4-dionenyl or imidazolidin-2,4-dionyl. It goes without saying that substitutents are only at positions where they are chemically possible, the person skilled in the art being able to decide (either experimentally or theoretically) without inappropriate effort which substitutions are possible and which are not.

Acyl is preferably a linear, branched, cyclic, cyclic-linear, saturated or partially or totally unsaturated organic carboxylic acid radical, especially unsubstituted or substituted alkoxycarbonyl, unsubstituted or substituted aryloxycarbonyl, unsubstituted or substituted aryl-lower alkoxycarbonyl, or preferably aryl-carbonyl, aryl-lower alkylcarbonyl or (unsubstituted or substituted alkyl)-carbonyl wherein aryl, alkyl and the substituents if present are preferably as defined above. Preferred is lower alkanoyl, especially formyl or more especially acetyl.

In unsubstituted or substituted alkyl, alkyl preferably has up to 20, more preferably up to 12 carbon atoms and is linear or branched one or more times; preferred is lower alkyl, especially C_1-C_4-alkyl. Substituted alkyl is especially lower alkanoyoxy-lower alkyl, such as acet-

oxymethyl, aryl-lower alkyl, especially benzyl, or lower alkanoyloxy-lower alkyl, e.g. acetoxymethyl.

Aryl is unsubstituted or substituted, and preferably has a ring system of not more than 24 carbon atoms, especially not more than 16 carbon atoms, is preferably mono-, bi- or tricyclic, and is unsubstituted or substituted preferably as defined above under "Substituted"; for example, aryl is selected from phenyl, naphthyl, indenyl, azulenyl and anthryl, and is preferably in each case unsubstituted or substituted phenyl. Unsubstituted aryl, preferably phenyl, is especially preferred.

In unsubstituted or substituted alkanesulfonyloxy, unsubstituted or substituted alkyl is preferably as defined above; preferred is unsubstituted or halogen substituted lower alkanesulfonyloxy, such as methanesulfonyloxy or trifluormethylsulfonyloxy.

In arylsulfonyloxy, aryl which can be unsubstituted or substituted is preferably as defined above, e.g. lower-alkyl subsituted phenyl; preferred is toluolsulfonyloxy.

Halogen or halo is preferably fluoro, chloro, bromo or iodo, most preferably chloro; bromo or iodo (if not stated otherwise).

Protecting groups, especially R2, especially for derivatising amino groups as in the case of R2, are generally known in sugar, amino acid and nucleotide chemistry, and they as well as methods for their introduction as well as their removal are described, for example, in standard text books (see J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973; Th. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides", Volume 3 (E. Gross and J. Meienhofer, eds.), Academic Press, London and New York 1981; "Methoden der organischen Chemie", Houben-Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974; and H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" ("Amino acids, peptides, proteins"), Verlag Chemie, Weinheim, Deerfield Beach and Basle 1982), which are incorporated by reference herein regarding these protecting groups, their introduction and/or their removal.

An R2-protected imino group may be protected, for example, by acyl (which can be removed e.g. by hydrolysis or reduction), arylmethyl (which can be removed by catalytic hydrogenation or reduction in the presence of hydrazine or sodium hypophospite or the like), unsubstituted or substituted lower alkyl, unsubstituted or substituted alkoxymethyl, etherified

mercapto, 2-acyl-lower alk-1-enyl, silyl, in the form of an N-lower alkylpyrrolidinylidene group or in the form of an azido group, or as substituted-sulfonyl amino, N,N-di-alkylformamidinyl (which can be removed e.g. with acid, such as HCl, or base, e.g. KOH), vinyl or allylamino. Preferred imino- and amino-protecting groups are lower alkoxycarbonyl, phenyl-lower alkoxycarbonyl, fluorenyl-lower alkoxycarbonyl, 2-lower alkanoyl-lower alk-1-en-2-yl and lower alkoxycarbonyl-lower alk-1-en-2-yl, with most preference being given to isobutyryl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, 3-methoxybenzyl, 2-nitrobenzyl, 2,4-dinitrophenyl, phenacyl, triphenylmethyl, benzoyl, tert-butoxycarbonyl, benzyloxycarbonyl, N-2-chloroethyl, N-(1-ethoxy)ethyl, tri-lower alkylsilyl, N-phenoxyacetyl, trichloroethyloxycarbonyl, cyclohexyloxycarbonyl, 1- or 2-adamantyl-oxycarbonyl, 4-tert-butylphenoxyacetyl, methoxymethyl, diethoxymethyl, chloroethoxymethyl, N,N-dimethylformamidinyl, mesitylenesulfonyl, p-methoxysulfonyl, benzenesulfonyl or N-methylpyrrolidin-2-ylidene, or the like.

It should be mentioned that also in other cases of reactions of the present inventions functional groups the participation of which in reactions is to be suppressed can be protected and deprotected at appropriate stages as required and/or desirable.

Where desired or necessary, compounds from intermediate reactions or the final reaction leading to the compound of the formula [A], or a salt thereof, can be purified or obtained in pure form according to standard procedures, such as evaporation, filtration, crystallization, chromatography, drying, extraction, acidification, alkalinization, centrifugation and the like.

Where necessary or desirable, reactions are conducted under an inert gas such as argon or nitrogen, and/or absolute solvents are used. Where elevated pressures are applied, the reaction, where required, takes place in a pressure vessel.

Where references (e.g. patent applications, patents or publications in journals) are mentioned hereinbefore and hereinafter, their content with respect to the reactions or compounds mentioned, respectively, are included by reference into the present disclosure.

Where a solvent or solvents are mentioned, this is intended to include also mixtures of solvents. Where not indicated that certain solvents are to be used, solvents may, for example, be selected from the following: The solvents from which those solvents that are suitable for any particular reaction may be selected include, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofurane or dioxane, liquid

aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

1,2,4-Triazolyl forming reagents are especially those that form with the R-NH-NH in 5-position of the indole ring in formula [B] a 5-(1,2,4-triazol-1-yl) moiety, with those in the following paragraph mentioned "as 1,2,4-triazolyl forming reagent" being preferred:

In the reaction of a compound [B] or a salt thereof to a compound of the formula [A] (especially Rizatriptan), or a salt thereof, the triazole ring formation (cyclisation) is preferably accomplished either (i) with Gold's reagent {[3-(dimethylamino)-2-azaprop-2-en-1-ylidene]-dimethylammonium chloride} as 1,2,4-triazolyl forming reagent, which is preferably used in equimolar or higher amounts related to the compound of the formula [B] or its salt, preferably in the presence of an appropriate solvent, such as a hydrocarbon, an ester or preferably a halogenated (especially chlorinated) hydrocarbon, such methylene chloride or trichloromethane, preferably at elevated temperatures, such as between 30 °C and reflux temperature of the reaction mixture, preferably under an intert gas such as nitrogen (for appropriate reaction conditions see e.g. Jenkins et al, J. Med. Chem. 35(13), 1992, 2392-2406, or US 4,556,717); or (ii) with 1,3,5-triazine as 1,2,4-triazolyl forming reagent, preferably in a 0.1- to 3-fold molar relationship to the compound of the formula [B], preferably in a (more preferably absolute) polar solvent, such as nitriles (e.g. acetonitrile) or alcohols, e.g. a lower alkanol, advantageously methanol or preferably ethanol, preferably at elevated temperatures, such as 30 °C to the reflux temperature of the reaction mixture (for appropriate reaction conditions see e.g. Grundmann et al., J. Org. Chem. 21, 1956, 1037-1038, or US 4,556,717); or (iii) with formamidine or preferably a formamidinium salt (e.g. the acetate or chloride) as 1,2,4-triazolyl forming reagent, preferably in more than equimolar amounts related to the compound of the formula [B], preferably in a polar solvent, e.g. a nitrile, such as acetonitrile, preferably at elevated temperatures, e.g. between 30 °C and the reflux temperature of the reaction mixture (for appropriate reaction conditions see e.g. Chem. Ber. 114, 1981, 2825-2833, and/or US 4,556,717); or (iv) with formamide, see

especially US 4,556,717 which is incorporated by reference here with regard to this type of reaction, or (v) any appropriate combination of two or more of the mentioned reaction conditions.

Where, prior to the ring formation with the 1,2,4-triazolyl forming reagent(s), removal of R = acyl is required, this is effected by standard hydrolysis procedures (preferred; e.g. in the presence of acid or preferably of base, e.g. alkaline metal hydroxide, such as sodium and/or potassium hydroxide, e.g. to remove R2 = acetyl or formyl) or further by catalytic hydrogenation, the latter preferably being directly effected when a compound of the formula [D], or a salt thereof, and/or a compound of the formula [E], or a salt thereof, each with R = acyl, is reacted under reductive conditions to the compound of the formula [B], or a salt thereof, as described above or in more detail below, so that a combination of these reaction steps forms an advantageous embodiment of the present invention.

Where desired, the conversion of salts into different salts, or of free compounds into the salts, of compounds of the formula [A] (or any other educts and intermediates for its synthesis) takes place in customary manner, for example by treatment with a suitable acidic agent or an ion exchange resin. Also the conversion of salts into the free compounds takes place according to standard conditions, where desired.

The reaction of a compound of the formula [D] to a compound of the formula [B] (or salts thereof, respectively) under reductive conditions preferably takes place in the presence of hydrogen and a (preferably heterogenous) catalyst, e.g. a Raney metal catalyst, preferably Raney-Ni or Raney-Co, or a noble metal on a carrier, e.g. Palladium on charcoal (Pd/C) or preferably Rhodium on charcoal (Rh/C), Platinum on charcoal (Pt/C) or Ruthenium on charcoal (Ru/C); in an appropriate solvent, such as an alcohol, e.g. a lower alkanol, such as methanol or ethanol, and/or an ester, such as a lower alkanoyl lower alkanoate, e.g. ethylacetate, in the absence or presence of water, preferably under elevated pressure (e.g. 2 to 200, preferably 30 to 80 bar hydrogen pressure), at customary temperatures, e.g. between 0 and 80 °C, e.g. at ambient (especially room) temperature. Appropriate conditions for the reduction are known (see e.g. US 4,557,717).

The reaction of the compound of the formula [D], or a salt thereof, to compound [A], or a salt thereof, can be led separately (e.g. in the case where the compound of the formula [D] is made from an aldehyde of the formula [O] as described above and particularly below, this combination of reactions thus forming a particularly advantageous embodiment of the pre-

sent invention), or it can take place as single step after or directly in combination (e.g. as one-pot reaction) with the reaction of a compound of the formulae [E] and [F] (or salts thereof, respectively), as described above and in particular below, so that this combination or the sequential reactions [E] + [F] -> [D] -> [B], especially further to [A], form a very advantageous embodiment of the present invention. The reaction conditions are preferably those described above for the reaction of a compound of the formula [D] to a compound of the formula [B][, with Pt/charcoal being less preferred as catalyst. For the conditions of conversion of a cyanide into a hydrazine those mentioned in US 4,556,717 are a useful example.

Also the separate reaction of [E] with [F] to [D] under reductive conditions preferably takes place with hydrogen under the reaction conditions mentioned above for the reaction of a compound of the formula [D] to a compound of the formula [B], with Pt/charcoal being less preferred as catalyst. As example preferably the conditions of conversion of a cyanide into a hydrazine mentioned in US 4,556,717 can be employed by way of analogy.

In the reaction of a compound of the formula [G], or a salt thereof, to a compound of the formula [E] with a cyanide salt, where preferably L is bromo or especially iodo, the cyanide salt is preferably a metal cyanide, especially selected from the group consisting of zinc cyanide ($Zn(CN)_2$) in the presence of a catalyst such as $Pd(dppf)Cl_2$, an alkyli metal cyanide in the presence of a Ni(0)-ccomplex, such as $Ni(PPh_3)$ which is preferably generated in situ from $Ni(PPh_3Cl_2$ by reduction with an additional metal such as manganese or zinc, see Bull. Chem. Soc. Jpn. 1988, 61, 1985, or preferably Copper(I)cyanide in NMP (N-methylpyrrolidone), where the Copper(I)cyanide is preferably used a molar excess, e.g. 1.1 to 2, for example about 1.5 equivalents; at a preferred temperature in the range from 100 to 220 °C, e.g. from 180 to 200 °C.

Alternatively, a compound of the formula [E] can also be obtained in accordance with the methods described in US 5,510,359

In the reduction of a compound of the formula [H] to a compound of the formula [G], or a salt thereof, or of a compound of the formula [C] to a corresponding compound of the formula [B] in the presence of borane, the borane is preferably obtained in situ from an alkali metal borohydride, especially sodium boro hydride, in the presence a lewis acid, especially a boron trihalogenide etherate, such as the boron trifluoride etherate with diethyl ether, and the reaction preferably takes place in an appropriate solvent, e.g. en ether, for example a di-lower alkoxy lower alkane, such as dimethoxyethane, die-ethylenglycol-di-methyl ether or a

cyclic ether, e.g. tetrahydrofurane, at preferred temperatures in the range from –20 to 50 °C, especially between -15 to 30 °C; the following reaction subjecting the resulting product(s) to removal of borane from any amino borane intermediates (which can preferably follow without isolation of the borane carrying intermediates, that is, as one-pot reaction; preferably after addition of a metal salt base, e.g. an alkali metal hydroxide in water, such as sodium or potassium hydroxide)) preferably takes place to an appropriate acceptor of the borane moiety or moieties to be removed, e.g. an amine, preferably with DABCO (diazabicyclo[2.2.0]octane) in an appropriate solvent, e.g. as just mentioned, where water may also be present if a metal salt base has been added, and preferably at eleated temperatures, e.g. between 50 °C and reflux temperature, for example at about 80 °C, and the subsequent oxidation/de-hydrogenation with an oxidant such as quinones or advantageously manganese dioxide (which is preferably conducted after partial isolation of the resulting product with some extraction steps) is preferably conducted in an appropriate solvent, e.g. an ether, such as a di-lower alkylether, e.g. tert.-butyl-methyl ether, preferably at temperatures between 10 °C and reflux temperature, e.g. between 20 and 50 °C.

The reaction of a compound of the formula [I] to a compound of the formula [H] with an electrophile capable of introducing group L, especially halogen by reaction with a halo-succinimide, especially N-chloro succinimide used to introduce chloro, preferably takes place in an appropriate solvent, e.g. a lower alkanoic acid, e.g. acetic acid, or a halogenated hydrocarbon, e.g. dichloroethane, and/or an aromatic solvent, e.g. chlorobenzene, a customary temperatures, e.g. from 10 to 40, such as from 20 to 30 °C.

The reaction of a compound of the formula [K] with a compound of the formula [L] (an active carbonic acid derivative wherein X is preferably chloro or bromo), to a compound of the formula [I] preferably takes place in the presence of a tertiary nitrogen base, preferably in an appropriate solvent, e.g. an ester, e.g. a cyclic ester, such as tetrahydrofurane, or preferably a lower alkyl-lower alkanoate, such as ethyl acetate, more preferably in the presence also of a N,N-di-(lower alkyl)-lower alkanoylamide, a lower alkanol, e.g. methanol or ethanol, or a di-lower alkylsulfoxide, e.g. dimethylsulfoxide, especially of N,N-dimethyl formamide (especially where one-pot sythesis from [M] via [K] to [I] is used, see below), preferably at temperatures from 10 °C to the reflux temperature or the reaction mixture, e.g. from 20 to 65 °C.

The reaction of a compound of the formula [M] to a compound of the formula [K] with malonic acid in the presence of a pyridine, especially pyridine (very preferred) and/or one or more

picolines, in the absence or presence of a N,N-di-(lower alkyl)-lower alkanoylamide (preferred), a lower alkanol, e.g. methanol or ethanol, or a di-lower alkylsulfoxide, e.g. dimethylsulfoxide, especially of N,N-dimethyl formamide, advantageously takes place in the presence of an ester, preferably a lower alkyl alkanoate, more preferably ethyl acetate, as a cosolvent, preferably at temperatures between 30 °C and reflux temperature, e.g. between 50 and 90 °C, for example between 60 and 80 °C, and is followed by conversion of the resulting compound which is present as a salt of a pyridine into the salt of the base NB given in formula [K], preferably by addition of the base NB to the reaction mixture (which in addition may also serve the reaction with a compound of the formula [L] in a subsequent reaction to produce a compound of the formula [I]) where the reaction of the isatine compound of the formula [M] and the conversion of the product salt of a pyridine into the corresponding salt of the formula [K] and more preferably also the reaction to give the compound of the formula [I] by reaction with a compound of the formula [L] preferably take place in the same reaction vessel.

A tertiary nitrogen base NB where the nitrogen is not part of a ring is preferably a nitrogen substituted by three moieties selected from alkyl, such as lower alkyl, especially ethyl, C_3-C_7-cycloalkyl, such as cyclohexyl, or phenyl-lower alkyl, such as benzyl. Preferred as base NB are N,N-dicyclohexyl-N-lower alkylamines, such as dicyclohexyl-ethylamine, or especially tri-lower alkylamines, such as triethylamine.

In the preferred alternative for synthesis of a compound of the formula [H], the reaction of a compound of the formula [K*] with a compound of the formula [L] to a corresponding compound of the formula [H] takes place under the conditions just described for reaction of a compound of the formula [K] with a compound of the formula [L] to a compound of the formula [I].

Also the reaction of a compound of the formula [M*] to a compound of the formula [K*], as well as the salt conversion, preferably takes place under the same conditions as just described for the synthesis of a compound of the formula [K] from a compound of formula [M]. Also here, the reaction of the isatine compound of the formula [M*] and the conversion of the product salt of a pyridine into the corresponding salt of the formula [K*] and more preferably also the subsequent reaction to give the compound of the formula [I] by reaction with a compound of the formula [L] preferably take place in the same reaction vessel.

Alternatively, a compound of the formula [B], or a salt thereof, can be obtained starting from a compound of the formula [C] – the reaction conditions are preferably the same as descri-

bed above for the conversion of a compound of the formula [H] to a compound of the formula [G].

The reaction of a compound of the formula [N] with a compound of the formula [F] (preferably with R = H) to a compound of the formula [C] preferably takes place under standard conditions for the hydrazinolysis of carbonic esters, e.g. in the presence of an appropriate solvent, such as an alcohol, e.g. a lower alkanol such as methanol, ethanol or isopropanol, preferably at elevated temperatures, e.g. between 50 °C and the reflux temperature of the reaction mixture, where preferably 0.5 to 5 equivalents of the hydrazine compound of the formula [F] is used in relationship to the compound of the formula [N].

The reaction of a compound of the formula [H] with carbon monoxide in the presence of the corresponding alcohol R_5-OH, preferably wherein R_5 is lower alkyl, e.g. ethyl or methyl, or benzyl, to a corresponding compound of the formula [N] takes place in the presence of a catalyst, preferably a homogenous Pd catalyst, e.g. $Pf(dppp)Cl_2$, and a tertiary nitrogen base, e.g. a tri-lower alkylamine, such as triethylamine, preferably in a polar solvent, e.g. an alcohol, such as ethanol, preferably takes place under elevated CO pressure, e.g. between 10 to 50 bar, preferably at elevated temperatures, e.g. from 40 to 150 °C, for example between 100 and 130 °C.

The reaction of an aldehyde of the formula [O], or a salt thereof, to a compound of the formula [B], or a salt thereof, with a hydrazine of the formula [F] can be conducted either under simultaneous reduction by way of reductive amination directly to a corresponding compound of the formula [B], or by first reacting with the hydrazine and then subsequent reduction of the resulting hydrazone of the formula [D]; the conditions are in each case standard conditions, for example, the reaction with simultaneous reduction (by reductive aminiation) preferably takes place under catalytic hydrogenation, e.g. with hydrogen in the presence of a heterogenous catalyst, such as a Raney-metal, e.g. Raney-Ni or Raney-Co, or a transition metal catalyst on a carrier, such as carbon, e.g. Pd/C, Ru/C, Rh/C or Pt/C, in an appropriate solvent, e.g. an alcohol, such as a lower alkanol, for example methanol or ethanol, preferably under pressure up to 15 MPa, preferably at temperatures from 5 to 100 °C; while in the reaction with sequential formation of a hydrazone of the formula [B] by first reacting with the hydrazine of the formula [F] to a corresponding hydrazone compound of the formula [D] that is then reduced to a compound of the formula [B], preferably the hydrazone is first formed by reaction of [O] and [F] (or salts thereof where present) in the presence of an appropriate

solvent, e.g. an aromatic solvent, such as toluene, or a polar solvent, e.g. an alcohol, such as a lower alkanol, e.g. methanol or ethanol, in the presence or absence of water, where required in the presence of an acid as catalyst, e.g. sulphuric acid, p-toluene sulfonic acid or formic acid, at preferred temperatures from 10 °C to the reflux temperature of the reaction mixture; subsequently, with or without partial or complete isolation, the resulting compound of the formula [D], or its salt, is then reduced by catalytic hydrogenation as just described, or alternatively with sodium borohydride, e.g. under the conditions described in *Carbohydr.Res.* **2000**, *327*(4), 463 which, in this regard, is incorporated by reference here.

The reaction [G] wherein L is halogen, especially iodo or bromo, or a salt thereof, by reacting it with first a lithium alkyl compound to form the lithio derivative and then with DMF (N,N-dimethyl formamide) or triethyl formate, plus hydrolysis to [O], preferably is accomplished under the following conditions: The lithiation is preferably performed in an ether solvent at a temperature from initially –70 to –30 °C to finally -10°C, and the lithiated species is then reacted with N,N-dimethyl.formamide (DMF), or triethyl orthoformate within a preferred temperature range from –20 to 60 °C. Hydrolysis of the intermediate product is preferably performed in a temperature range from 0-100 °C, more preferably in the range from 20-80 °C. A further variant to obtain a compound of the [O] is described in US 5,510,359.

R2 = acyl can be introduced in any compound with a indole nitrogen in 1-position of the indole ring system mentioned hereinbefore and hereinafter at every appropriate stage, e.g. by reaction with a symmetric acid anhydride of the acid forming the basis for an acyl group R2 or a mixed anhydride, preferably an anhydride of an alkanoic acid, in the presence or absence of a further solvent, at elevated temperatures, especially under reflux.

Starting materials or reagents for which the synthesis is not mentioned explicitely in the present disclosure (such as compounds of the formula [F], or salts thereof) are commercially available, prepared according to standard methods or known in the art.

Where compounds (or salts thereof) are mentioned above as embodiments of the invention, these are especially important as intermediates for the synthesis of compounds of the formula [A], or salts thereof, and thus for the synthesis of tryptophanes or related compounds.

Where educts or intermediates are used, the products of their reaction are, regarding their moieties, corresponding to the used intermediates or educts, if not indicated otherwise.

Preferred embodiments of the invention:

The invention relates to the single reaction steps as given above or below, as well as any combination of two or more reaction sequence steps that are in succession, that is, where the product of one reaction is the precursor of the next reaction that is part of such combination.

Where subsequently formulae are mentioned, this is intended to refer to the formulae given above, respectively.

Especially preferred is the combination of the reaction of a compound of the formula [D] to a compound of the formula [B] that is then reacted to a compound of the formula [A] as described above or below, where preferably the compound of the formula [D] is produced by reaction of a compound of the formula [E] with an compound of the formula [F], where preferably the compound of the formula [E] is obtained by reaction of a compound of the formula [G], which is preferably obtained from a compound of the formula [H], which is preferably obtained either (a) from a compound of the formula [I] that is preferably obtained from a compound of the formula [K] by reaction with a compound of the formula [L], where the compound of the formula [K] is preferably obtained from a compound of the formula [M]; or (ii) from a compound of the formula [K*] by reaction with a compound of the formula [L], where the compound of the formula [K*] is preferably obtained from a compound of the formula [M*]; in each case preferably under the (especially the more preferred) reaction conditions described above or below; where for each compound, where salt-forming groups are present, the free compound or a salt thereof may be used or produced.

Alternatively, especially preferred is the combination of the reaction of a compound of the formula [C] to a compound of the formula [B] that is then reacted to a compound of the formula [A] as described above or below, where preferably the compound of the formula [C] is produced by reaction of a compound of the formula [N] with a acompound of the formula [F], where preferably the compound of the formula [N] is obtained from a compound of the formula [H] which is preferably produced by one of the two ways described in the last paragraph; in each case preferably under the (especially the more preferred) reaction conditions described above or below; where for each compound, where salt-forming groups are present, the free compound or a salt thereof may be used or produced.

In still another alternative way, the combination of the reaction of a compound of the formula [O] with a compound of the formula [F] to a compound of the formula [D] that is then reacted to a compound of the formula [A] as described above or below is preferred; in each case preferably under the (especially the more preferred) reaction conditions described above or below; where for each compound, where salt-forming groups are present, the free compound or a salt thereof may be used or produced.

The invention also relates especially to the following intermediates in the synthesis of a compound of the formula [A], or precursors therefore:

A compound of the formula [B], wherein R is lower alkanoyl, especially formyl or acetyl, or preferably hydrogen, R2 is hydrogen and each of R3 and R4 is methyl, or a salt thereof

A compound of the formula [C], wherein R is lower alkanoyl, especially formyl or acetyl, or preferably hydrogen, R2 is hydrogen and each of R3 and R4 is methyl, or a salt thereof.

A compound of the formula [D], wherein R is lower alkanoyl, especially formyl or acetyl, or preferably hydrogen, R2 is hydrogen, and each of R3 and R4 is methyl, or a salt thereof.

A compound of the formula [G], wherein R2 is hydrogen and each of R3 and R4 is methyl, or (less preferably) a salt thereof.

Preferred embodiments of the invention can be found in the claims, which are incorporated here by reference, the dependent claims representing preferred embodiments of the invention. In the claims, more general definitions can be replaced with the more specific definitions given above, independently or together with some or all other general expressions used in the same claim, respectively, thus leading to further preferred embodiments of the invention.

Highly preferred embodiments of the invention are those where in the processes mentioned above the formulae represented above are replaced with the corresponding specific compounds mentioned in the examples.

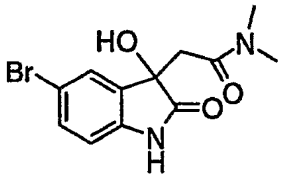
Very preferred process steps, combinations of process steps, novel starting materials and intermediates (compounds) that are part of the present invention are described in the subsequent examples, thus forming very preferred embodiments of the invention.

Examples:

The following examples serve to illustrate the invention without limiting the scope thereof. Wherever ambient temperature or room temperature is mentioned or no temperature is given, this denotes a temperature in the range 20-25°C.

The subsequent Reference Examples are from Ciba Patent Application PCT/EP03/50992 the examples of which, especially regarding intermediates and final products falling under any of the formulae of the present invention, are here incorporated by reference as reference examples).

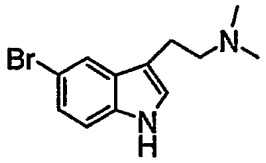
Reference Example 1: Preparation of 2-(5-Bromo-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-*N,N*-dimethyl-acetamide:



A 2 L flask fitted with an inner thermometer, mechanical stirrer, and reflux condenser is charged with 5-bromo-isatin (100 g, 0.442 mol), malonic acid (55.2 g, 053 mol), pyridine (100.6 g, 1.274 mol), dimethyl formamide (80 g), and ethyl acetate (100 g). When the temperature of the mixture reaches 60°C, the bromo isatin starts to dissolve, and a deep red mixture forms. Carbon dioxide starts to evolve, and after about 45 minutes the precipitation of the intermediate pyridinium (5-bromo-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-acetate starts. The reaction mixture is kept at 80°C for another 3 hours. Then triethyl amine (49.2g, 0.486 mol) iss added, and the pyridinium salt dissolves to give a deep brown solution. This solution is allowed to cool to 50°C, and then a solution of dimethyl carbamoyl chloride (48 g, 0.442 mol, **CAUTION:** carcinogen) in 40 g of ethyl acetate is added dropwise during 30 minutes. Carbon dioxide evolves, and the temperature rises to 60°C. After about 45 minutes, the product starts to precipitate from the reaction mixture. The mixture is kept at 60°C for another hour, and then water (500 mL) and 36% HCl (250 mL, 4 mol) are added in that order during 10 minutes. The product is filtered off , and reslurried in an mixture of acetone/water (500 mL, 1:1, v:v). The slurry is filtered again, and the product is finally dried to give the title compound as a gray powder which is of suitable purity for direct use in the further steps. Yield: 75.2 g (54.2%). An analytically pure sample is obtained by recrystallization from

methanol, mp = 245-246°C, dec. ^{1}H-NMR (DMSO-D6, 300 MHz): δ 2.64 (s, 3, CH_3), 2.93 (s, 3, CH_3), 2.93, 3.27 (AB, 2, ^{2}J = 16.5 Hz, CH_2), 6.01 (br s, 1, OH), 6.73 (d, 1, ^{3}J = 8.2 Hz, H-7), 7.30 (dd, 1, ^{3}J = 2.0 Hz, H-6), 7.42 (d, 1, H-4), 10.18 (br s, 1, NH). ^{13}C-NMR (DMSO-D6, 75 MHz) δ 35.04, 37.45 ($N(CH_3)_2$), 40.78 (CH_2), 73.90 (C-3), 111.85 (C-7), 113.29 (C-5), 127.03 (C-4), 131.83 (C-6), 135.78 (C-9), 143.18 (C-8), 168.93 (*C*ONMe_2), 178.68 (C-2).

Reference Example 2: Preparation of [2-(5-Bromo-1*H*-indol-3-yl)-ethyl]-dimethyl-amine:

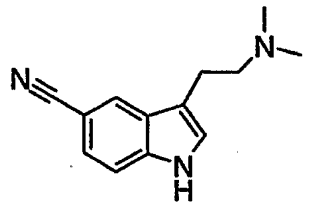


A 1 L flask is charged with 2-(5-bromo-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-*N,N*-dimethyl-acetamide (Reference Example 1) (31.2 g, 0.1 mol), sodium borohydride (11.8 g 96%, 0.3 mol), and 250 mL of dimethoxyethanol (DME). The mixture is cooled to -15°C, and to the stirred suspension, BF_3-etherate (56.6 g, 0.4 mol) is added dropwise. The temperature is maintained between -15 and -10°C during the exothermic addition. The mixture is then allowed to warm slowly to ambient temperature (25-27°C), and left stirring over night. The mixture is cooled with an ice bath and quenched by the addition of 4N NaOH (200 mL). The formed viscous emulsion is heated to 80°C for 30 minutes, then diazabicyclo[2.2.2]cyclooctane (DABCO) (12.7 g 97%, 0.11 mol) is added, and then the mixture is heated for two additional hours under reflux. After cooling to ambient temperature, the aqueous layer is removed and the organic layer is extracted twice with each 50 mL of a 4 N NaOH.solution. After re-extraction of the combined inorganic layers with toluene (150 mL), the aqueous phase is disposed off, and the toluene layer is added back into the reaction vessel. To the vessel, additional toluene (150 mL) is added and the mixture is then extracted with water (200 mL). The aqueous layer is separated, and extracted twice with each 150 mL of toluene. After disposal of the inorganic the combined toluene layers are extracted for three times with water (300mL, 2 x 150 mL), and the aqueous layer is again discarded. The toluene layer is then extracted twice with 4N HCl (100mL and 50 mL). Using the combined acidic extracts, the pH is then adjusted to 14 by the addition of 4 N NaOH. Then the aqueous layer is extracted twice with tert-butyl methyl ether TBME (150 mL and 50 mL), and the combined extracts are washed with brine (50 mL) and then transferred into a 500 mL flask. To the stirred TBME solution, MnO_2 (34.8 g, 0.4 mol) is then added, and temporarily the temperature rises to 40°C. After one hour the aniline by-product has been converted completely, and then the MnO_2 is filtered off. Removal of the solvent from the filtrate gives the title product as a colourless viscous oil

which crystallizes (23.85 g, 85%), mp = 95-96°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.37 (s, 6 H, 2 CH3), 2.27 (m, 2 H, $C\underline{H}_2CH_2NMe_2$), 2.90 (m, 2 H, $CH_2C\underline{H}_2NMe_2$), 6.86 (d, 1 H, ^{3}J = 1.8 Hz, H-2), 7.03 (d, 1 H, ^{3}J= 8.8 Hz, H-7), 7.21 (dd, 1 H, ^{4}J = 1.8 Hz, H-6), 7.70 (d, 1 H, H-4), 9.36 (br s, 1 H, H-1). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.60 ($\underline{C}H_2CH_2NMe_2$), 45.47 ($N(\underline{C}H_3)_2$), 60.25 ($CH_2\underline{C}H_2NMe_2$), 112.42 (C-5), 112.98 (C-7), 113.54 (C-3), 121.39 (C-4), 123.61 (C-2), 124.64 (C-6), 129.43 (C-8), 135.36 (C-9).

NMR-data of the intermediate side-product 2-(2-amino-5-bromo-phenyl)-4-dimethyl-amino-butan-1-ol, which is formed by ring opening/reduction: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.60-1.77, 1.89-2.10 (2 m, 1 H each, CH_2); 2.23 (s, 6 H, $N(CH_3)_2$); 2.24-2.41 (m, 2 H, CH_2NMe_2); 3.18-3.24 (m, 1 H, CH_2OH); 3.24-3.34 (m, 1 H, CH); 3.64-3.70 (m, 1 H, CH_2OH); 3.73 (br s, 1 H, OH); 6.46 (d, 1 H, 3J = 8.2 Hz, Ar H-3); 7.08 (dd, 1 H, 4J = 2 Hz, Ar H-4); 7.14 (1 H, Ar H-6). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 32.33 (CH_2); 40.44 (CH); 45.72 ($N(CH_3)_2$); 53.88 CH_2NMe_2); 57.63 (CH_2OH); 110.25 (Ar C-1); 110.89 (Ar C-3); 127.05, 130.83 (Ar C-4, C-6); 135.50 (Ar C-5); 150.64 (Ar C-2).

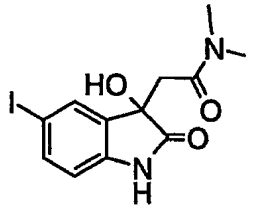
Reference Example 3: Preparation of 3-(2-dimethylamino-ethyl)-1*H*-indole-5-carbonitrile



Under an inert atmosphere a flask is charged with [2-(5-bromo-1*H*-indol-3-yl)-ethyl]-dimethyl-amine (Example 3) (1.0 g, 3.74 mmol), zink cyanide (0.235 g, 2 mmol), $Pd_2(dba)_3xCHCl_3$ (0.194 mg, 5 mol%), dppf (bis-diphenylphosphino ferrocene) (0.207 g, 0.374 mmol, 10 mol %), and DMF (12 mL). The orange slurry is heated to 110°C and stirred for 21 hours. To the black suspension, which has formed, THF (100 mL) is added, and this is extracted with 1 N NaOH (100 mL). The organic layer is washed with water twice (50 mL each), dried and removal of the solvent gives the title product (0.67 g, 84%) as brown solid.

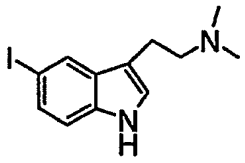
^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 6 H, 2 CH_3); 2.67 (m, 2 H, CH_2NMe_2); 2.91 (m, 2 H, CH_2); 7.01 (s, 1H, H-2); 7.13 (d, 1 H, ^{3}J = 8.3 Hz, H-7); 7.26 (dd, 1 H, ^{4}J = 1.6 Hz, H-6); 7.87 (d, 1 H, H-4); 9.80 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.48 (CH_2); 45.42 (CH_3); 60.06 (CH_2N); 101.75 (C-5); 112.24 (C-7); 114.74 (C-3); 121.41 (CN); 124.49 (C-4); 124.62 (C-6); 124.75 (C-2); 127.31 (C-9); 138.47 (C-8).

Reference Example 4: 2-(3-Hydroxy-5-iodo-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-*N,N*-dimethyl-ac tamid



A 2 L flask with mechanical stirrer is charged with 5-iodo-isatin (78.1 g, 0.286 mol), malonic acid (35.7 g, 0.343 mol), and pyridine (90.4 g, 1.144 mol). The mixture is heated to 80°C. When most of the isatine has dissolved, ethyl acetate (100 mL) is added to prevent blocking of the stirrer by the precipitating pyridinium (3-hydroxy-5-iodo-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-acetate. After 1 hour, precipitation of the latter salt starts, and when the mixture has been kept stirring for another 2 hours, a suspension of the salt in an orange solution has formed. To this is added triethyl amine (43.3g, 0.429 mol), and the salt dissolves to give a dark solution. Then a solution of dimethyl carbamoyl chloride (40 g, 0.372 mol) in ethyl acetate (50 mL) is added dropwise during 20 minutes. A solid starts to precipitate, and the mixture is stirred for another 2 hours at 80°C. Then 4 N HCl is added (350 mL), and stirring is continued for 30 additional minutes in order to hydrolyze any excess carbamoyl chloride. The mixture is then filtered, and the filter cake is washed with 50% ethanol and then with water. After drying 72.6 g (70.5%) of a grayish powder of the title compound, mp. = 246°C. ^{1}H-NMR (DMSO-D6, 300 MHz) δ 2.62, 2.91 (2 s, 3 each, $N(CH_3)_2$); 2.91, 3.25 (AB, 2 H, ^{2}JI = 16.4 Hz, CH_2); 5.97 (br s, 1 H, OH); 6.59 (d, 1 H, ^{3}J = 7.9 Hz, H-7); 7.46 (dd, 1 H, ^{4}J = 1.5 Hz, H-6); 7.54 (d, 1 H, H-4); 10.15 (br s, 1 H, NH). ^{13}C-NMR (DMSO-D6, 75 MHz) δ 35.08, 37.48 ($N(CH_3)_2$); 40.86 (CH_2); 73.76 (C-3); 84.29 (C-5); 112.49 (C-7); 132.44 (C-4); 136.06 (C-9); 137.72 (C-6); 143.66 (C-8); 168.93 $CONMe_2$); 178.47 (C-2).

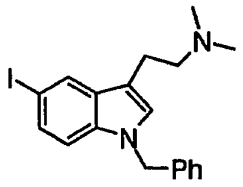
Reference Example 5: Preparation of [2-(5-Iodo-1*H*-indol-3-yl)-ethyl]-dimethyl-amine:



A 3 L flask is charged with 2-(5-iodo-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-*N,N*-dimethyl-acetamide (Reference Example 4) (100 g, 0.277 mol), and 800 mL of DME. The supension is cooled to -15°C, and sodium borohydride (31.5 g 96%, 0.832 mol) is added to this mixture, which causes a raise of the temperature by 5°C. To this, BF_3-etherate is added

dropwise during 30 minutes (157.6 g, 1.11 mol). Initially there is a strong exothermic reaction (requires slow addition of BF3-etherate) and evolution of a gas. The temperatureis maintained between -15 and -10°C during the addition. The formed orange slurry is then allowed to warm slowly to ambient temperature (25-27°C), and left stirring over night (17 h). To this mixture, then 4N NaOH (555 mL) is added and the mixture is heated under reflux for 50 minutes. Then DABCO (34.3g) is added, and refluxing the mixture is continued for two additional hours. Then water (250 mL) is added, and the DME is removed on the rotavapor. The obtained orange slurry is then extracted with TBME (1000 mL, 2x 600 mL), and the combined organic layers are washed with water (800 mL) and brine (700 mL), and concentrated on the rotavapor to about 600 mL. To the stirred residue, MnO_2 (72.4 g), is added, and the exothermic oxidation causes a temperature rise of 20°C. Stirring is continued for one hour, and then the MnO_2 is filtered off. Removal of the solvent from the filtrate gives a brown oil, which is dissolved in toluene. The toluene is extracted for three times with 4 N HCl (300 mL, 2 x 150 mL). After adjustment of the pH of the combined aqueous layers to about 10, the product is re-extracted with TBME (3 x 700 mL). The combined organic layers are washed with water (500 mL), and brine (500 mL), and after almost complete removal of the solvent on the rotavapor and standing over night at 4°C some of the product crystallizes (39g, 44.7%). Further concentration of the mother liquors and standing for two additional days gives another crop of the title product (9.5 g, 10.9%), while still about 20 g of material (about 22%) remains in the mother liquors. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.34 (s, 6 H, NMe_2); 2.59-2.66 (m, 2 H, CH_2NMe_2); 2.85-2.92 (m, 2 H, $ArCH_2$); 6.90 (d, 1 H, ^3J = 2.2 Hz, H-2); 7.03 (d, 1 H, ^3J = 8.4 Hz, H-7); 7.38 (dd, 1 H, ^4J = 1.3 Hz, H-6); 7.91 (d, 1 H, H-4); 8.56 (br s, 1 H, NH). ^{13}C-NMR ($CDCl_3$-D6, 75 MHz) δ 23.71 ($ArCH_2$); 45.65 ($N(CH_3)_2$); 60.32 (CH_2NMe_2); 82.77 (C-5); 113.36 (C-6); 113.86 (C-3); 122.78 (C-2); 127.87 (C-4); 130.29 (C-7); 130.33 (C-8); 135.62 (C-9).

Reference Example 6: Preparation of [2-(1-Benzyl-5-iodo-1*H*-indol-3-yl)-ethyl]-dimethyl-amine:

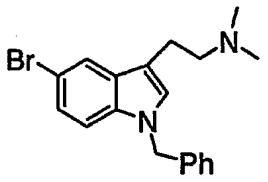


To a solution of [2-(5-iodo-1*H*-indol-3-yl)-ethyl]-dimethyl-amine (Reference Example 5) (35.0 g, 111.4 mmol) in DMF (250 mL), sodium hydride is added (2.81 g, 117 mmol) at RT in portions during 15 minutes. The mixture is then stirred for another 15 minutes, and then

cooled to 4°C. A solution of benzyl chloride (14.1 g, 111.4 mmol) in DMF (50 mL) is added during 20 minutes, and the temperature is maintained during 4 to 8°C. The mixture is left stirring over night, and then most of the solvent is removed on the rotavapor. To the residue is added water (500 mL), and the product is extracted with TBME (2 x 250 mL). The organic layer is washed with brine (2 x 250 mL), and after removal of the solvent, 28.5 g of a brown oil is obtained. This is dissolved in ethyl acetate (500 mL) and the product is extracted with 4 N Hcl (550 mL). The product is liberated by adding 30% NaOH to the aqueous layer (300 mL), and re-extracted into ethyl acetate (500 mL). The organic layer is washed with brine (2 x 250 mL), and the solvent removed to leave 20.2 g of brown oil, which is crystallized from di-isopropyl ether and pentane to give the title product (17.3 g, 38%). Concentrating the aqueous layer of the first gives a precipitate (18.8 g), which is recrystallized from ethyl acetate (250 mL) to give 12.3 g of the N-benzyl ammonium chloride of the target.

Reference Example 7:

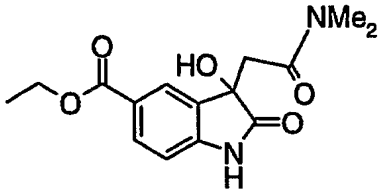
Preparation of [2-(1-Benzyl-5-bromo-1*H*-indol-3-yl)-ethyl]-dimethyl-amine:



In a 100 mL flask with inner thermometer and stirrer, 3.76 g (14.1 mmol) of [2-(5-bromo-1H.-indol-3-yl)-ethyl]-dimethyl-amine (Example 3) is dissolved in 40 mL of dry N,N-dimethyl formamide (DMF). To the solution NaH (95%, 366 mg, 14.5 mmol) is added under an inert atmosphere. Hydrogen gas is forming, and the NaH dissolves under slight warming during about 30 minutes. The solution is then cooled to 5°C, and a solution of benzyl chloride (1.77 g, 14 mmol) in 10 mL of DMF is added dropwise during a 10-minute period. The cooling bath is removed, and the mixture is left stirring over night at ambient temperature. Then the mixture is diluted with water (about 100 mL) and extracted with n-hexane/ether (about 1:1, 3 x 100 mL), and the combined organic extracts are re-extracted with water (3 x 100 mL). After drying and removal of the solvent, the remaining oil is chromatographed on silica (80 g, 230-400 mesh, ethyl acetate/ethanol 5:2 + 1% NH_3) to give 3.86 g (76.6%) of the title product as an oil which crystallized on standing, mp = 54-55°C. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.33 (s, 6 H, $N(CH_3)_2$); 2,57-2.65, 2.86-2.94 (2 m, 2 H each, CH_2CH_2); 5.23 (s, 2 H, CH_2Ph); 6.96 (s, 1 H, H-2); 7.05-7.08 (m, 2 H, Ph-H) 7.14 (d, 1 H, ^3J = 9Hz, H-7); 7.22 (dd, 1 H, ^4J = 2 Hz, H-6); 7.25-7.33 (m, 3 H, Ph-H); 7.74 (d, 1 H, H-4). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.85 (CH_2); 45.77

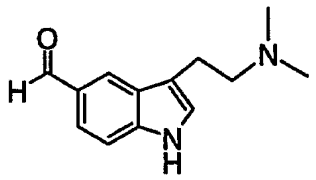
($N(CH_3)_2$); 50.31 (NCH_2); 60.55 (CH_2Ph); 111.40, 112.58, 113.70, 121.90, 124.74, 126.91, 127.13, 127.93, 129.03, 130.20 135.52, 137.50.

Reference Example 8: Preparation of 3-Dimethylcarbamoylmethyl-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indole-5-carboxylic acid ethyl ester:



A pressure vessel is charged with 2-(5-Bromo-3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)-*N,N*-dimethyl-acetamide (Reference Example 1) (21.92g, 70 mmol), Pd(dppp)Cl2 (4.13g, 7 mmol), triethyl amine (28.4g, 0.28 mol) and ethanol (405 ml, solvent). After assembling and purging with nitrogen, the vessel is charged with carbon monoxide to a pressure of 20 bar, and the carbonylation is performed at 120°C over night. The reaction mixture is filtered through a celite pad, and the solvent is removed on the rotavapor. The residue is kept under reflux with ethyl acetate (750 mL), and filtered. After washing the filter cake for three times with ethyl acetate (3 * 100 mL), the filtrate is concentrated (to ca. 300 mL), and the obtained suspension is left at 0°C over night. The product is filtered off and dried to give 19.0 g (87%) of the title compound in the form of beige crystals. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.29 (tr. 3 H, J = 7.0Hz); 2.62, 2.94 (2 s, 3 each, $N(CH_3)_2$); 2.98, 3.32 (AB, 2J = 18.2 Hz, CH_2NMe_2); 4.17-4.34 (m, 2 H, CH_2Me); 6.02 (s, 1 H, OH); 6.82 (d, 1 H, J = 7.6 Hz, H-7); 7.79 (br s, 1 H, H-4); 7.81 (dd, 1 H, J = 7.6 Hz, J = 1.8 Hz, H-6). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 15.16 (CH_3); 35.13, 37.56 ($N(CH_3)_2$); 46.49 (CH_2NMe_2); 61.02 (CH_2Me); 73.56 (C-3); 109.75 (C-7);123.16, 124.73 (C-6); 131.72 (C-4); 133.49, 148.53 (C-8); 166.34, 168.78, 179.23 (3 C=O).

Reference Example 9: Preparation of 3-(2-Dimethylamino-ethyl)-1*H*-indole-5-carbaldehyde

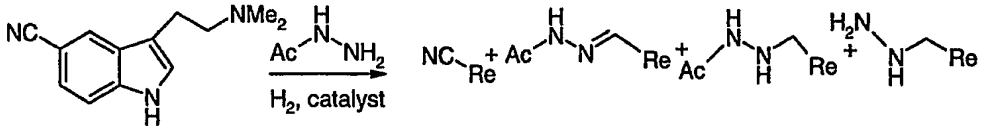


To a solution of [2-(5-bromo-1*H*-indol-3-yl)-ethyl]-dimethyl-amine (Reference Example 2) (15 g, 56.1 mmol) in ether (450 mL), at –75°C a solution of *tert*-butyl lithium (99 ml of 1.7 N solution in hexanes, 168 mmol) is added. The mixture is stirred for 50 minutes at -75°C, and

then for 30 minutes at –30°C. To the obtained beige suspension, DMF (22.5 ml) is added during 15 minutes, and then the mixture is allowed to warm to ambient temperature. The mixture is poured on water and extracted with diethyl ether (500 mL). After washing the organic layer with brine (3 times 500 mL), and drying (sodium sulfate), removal of the solvent leaves the crude aldehyde, which is recrystallized, from toluene/hexane. Yield of the title compound: 9.9 g (81.8%) yellowish plates, mp = 103°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 6 H, $N(CH_3)_2$); 2.65-2.75 (m, 2 H, CH_2); 2.96-3.03 (m, 2 H, CH_2NMe_2); 7.08 (d, 1 H, 3J = 2.7 Hz, H-2); 7.33 (d, 1 H, ^{3}J = 8.4 Hz, H-7); 7.70 (dd, 1 H, ^{4}J = 1.7 Hz, H-6); 8.13 (d, 1 H, H-4); 8.74 (br s, 1 H, NH); 10.02 (s, 1 H, CHO). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 23.91 (CH_2); 45.76 (CH_3); 60.40 (CH_2N); 111.85 (C-7); 116.68 (C-3); 122.87 (C-6); 123.61 (C-2); 124.04 (C-4); 127.68 (C-9); 129.35 (C-5); 140.06 (C-8); 192.56 (CHO).

Where in the following Examples HPLC is mentioned, the following conditions apply:
Column: Hypersil BDS-C18, 125 x 4 mm, eluent: Flow 1 ml/min, acetonitrile:water gradient 1 % acetonitile in water to 100 % acetonitrile within 10 min, then 2 min 100 % acetonitrile, 0,1 % trifluoroacetic acid as additive during the whole elution, detection: UV at 254 nm; retention times: 3-(2-dimethylamino-ethyl)-1H-indole-5-carbonitrile 4.7 min; [2-(5-Bromo-1*H*-indol-3-yl)-ethyl]-dimethyl-amine (Reference Example 2): 5.7 min; [2-(5-Iodo-1*H*-indol-3-yl)-ethyl]-dimethyl-amine (Reference Example 5): 5.7 min

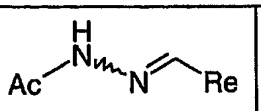
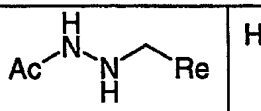
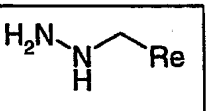
Example 1: Reductive hydrazination of 3-(2-dimethylamino-ethyl)-1H-indole-5-carbonitrile to the corresponding hydrazone and hydrazine



A glass vial is charged with 3-(2-dimethylamino-ethyl)-1H-indole-5-carbonitrile (Reference Example 3, Example 3 or Example 4; 100 mg, 0.47 mmol), N-acetyl hydrazine (39 mg, 0.47 mmol) and catalyst (see table). After flushing the vial with argon, methanol (3 ml) is added, and the vial transferred into an autoclave. The autoclave is purged thrice with nitrogen and

then thrice with hydrogen. After a check for tightness, the hydrogenation is performed at 55bar/105°C over night. The hydrogen is then released, and the catalyst is removed via filtration through a millipore syringe filter. The clear filtrate is analysed by HPLC for the products the retention times are given in the table below.

The following table shows the yields when different catalysts are used:

Catalyst	**Educt**			
Retention-time HPLC		4.1 min	3.6 min	3.3 min
Raney-Ni	2%	13%	30%	55%
Ru/C (10%)	2%	37%	12%	49%
Rh/C (5%)	2%	44%	15%	36%

Example 2: Preparation of Rizatriptan:

A solution of [2-(5-Hydrazinomethyl-1H-indol-3-yl)-ethyl]-dimethyl-amine (3.1g, 85% purity, 11.9 mmol) and 1,3,5-triazine (0.69g, 8.5 mmol) in ethanol (50 ml) is refluxed over night. The solution is then diluted with tert-butyl methylether (TBME), and the precipitated ammonium salts are filtered off. Removal of the solvent on the rotavapor produces 3.6g of an oil which is chromatographed on silica (CH_2Cl_2: MeOH:NH_4OH 98:2:1 to 95:5:1 v:v:v) to give 1.75g (55%) of the product, dimethyl-[2-(5-[1,2,4]triazol-1-ylmethyl-1H-indol-3-yl)-ethyl]amine (Rizatriptan). HPLC retention time: 4.0 min.

Example 3: Synthesis of N,N-dimethyl 2-(5-cyano-1H-indol-3-yl)ethyl-amine

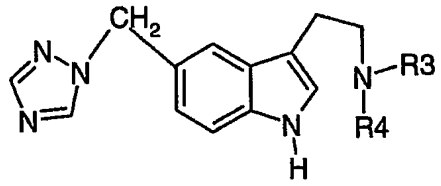
A flask with mechanical stirrer is charged with 5-iodo-dimethyltryptamine (179g of 75% purity, 0.427 mol), copper (I)cyanide (90g, 1.0mol), and N-methyl pyrrolidone (1.5 l). The pink suspension is heated at 180°C under a nitrogen atmosphere and vigorously stirred, until the iodide is completely consumed (7 h). After cooling to ambient temperature ammonia (2 l 25% solution in water) is added, and the resulting mixture is stirred over night. The mixture is then extracted with TBME (6* 1.5 l), and the combined organic layers are washed with water (3 * 3 l), and brine (1 * 3 l), and dried (sodium sulfate). Removal of the solvent leaves 75g (82%) of the product which is >95% pure by HPLC (other properties cf. Reference Example 3).

Example 4: Synthesis of N,N-dimethyl 2-(5-cyano-1H-indol-3-yl)ethyl-amine

A flask is charged with 5-bromo-dimethyltryptamin (5.34g, 20mmol), copper (I)cyanide (2.69g, 30mmol), and N-Methylpyrrolidone (20 ml). The mixture is heated at 200°C for 9 hours under a nitrogen atmosphere and then left stirring over night. The brown mixture is poured on water to give a brown precipitate. This is suspended in ammonia (100 ml 25% solution in water), and the mixture is stirred over night. Extraction with TBME (3* 100 ml), and removal of the solvent from the dried (sodium sulfate) organic layer gives the title product as a yellow solid (properties as in Reference Example 3).

Claims:

1. A process for the manufacture of an 1,2,4-triazol-1-yl compound of the formula [A],



[A]

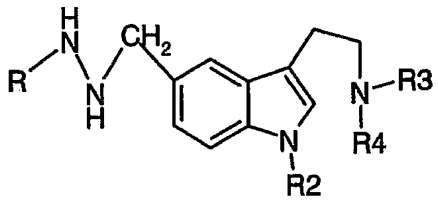
or a salt thereof,

wherein

each of R3 and R4 is hydrogen or lower alkyl

said process comprising

reacting a hydrazine compound of the formula [B]



[B]

wherein

R is hydrogen or acyl

R2 is hydrogen or a protecting group, and

R3 and R4 have the meanings as defined above for compounds of the formula [A],

or a salt thereof,

with a 1,2,4-triazolyl forming reagent,

and, if R is acyl in formula [B], removing an acyl group R before the reaction of the compound of the formula [B] with the 1,2,4-triazolyl forming reagent,

and removing any protecting group R2 to produce the compound of the formula [A], or a salt thereof.

2. The process according to claim 1 for the manufacture of Rizatriptan.

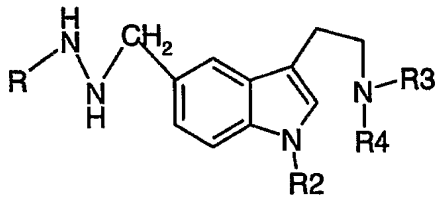
3. The process according to claim 1, comprising the additional step of converting a salt of a resulting compound of the formula [A] into a free form of a compound of the formula [A],

converting a resulting free form of a compound of the formula [A] into a salt, or converting a salt of a compound of the formula [A] into a different salt.

4. The process according to claim 1, where R in the compound of formula [B] is hydrogen and/or lower alkanoyl, and lower alkanoyl is hydrolytically removed prior to the reaction with the 1,2,4-triazolyl forming reagent, and where in each of formulae [A] and [B] each of R3 and R4 is methyl and the compound of the formula [A] is produced in free form or in the form of a pharmaceutically acceptable salt.

5. The process according to claim 4, where R in the compound of formula [B] is hydrogen or acetyl or formyl, and formyl or acetyl is hydrolytically removed prior to the reaction with the formamidinium salts or derivatives.

6. A process for the manufacture of a compound of the formula [B] as shown in claim 1



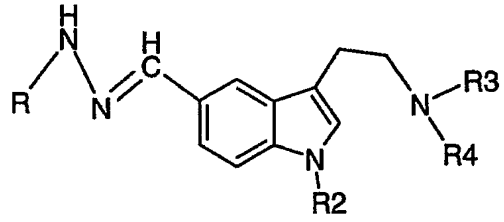
[B]

wherein

R is hydrogen or acyl

R2 is hydrogen or a protecting group, and each of R3 and R4 is hydrogen or lower alkyl, or a salt thereof,

comprising reacting a compound of the formula [D],

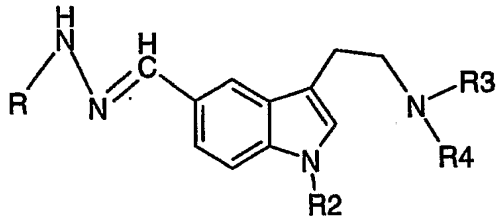


[D]

wherein R, R2, R3 and R4 are as defined above, or a salt thereof, under reductive conditions to a compound of the formula [B], or a salt thereof.

7. Process of claim 6, wherein R is hydrogen or lower alkanoyl, and each of R3 and R4 is methyl.

8. A process for the manufacture of a compound of the formula [D] as shown in claim 6,

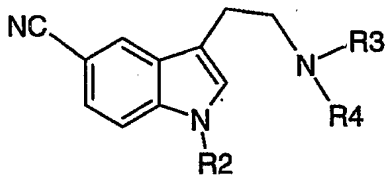


[D]

wherein

R is hydrogen or acyl, R2 is hydrogen or a protecting group, and each of R3 and R4 is hydrogen or lower alkyl, or a salt thereof,

comprising reacting a compound of the formula [E],



[E]

wherein each of R2, R3 and R4 is as defined above, or a salt thereof,

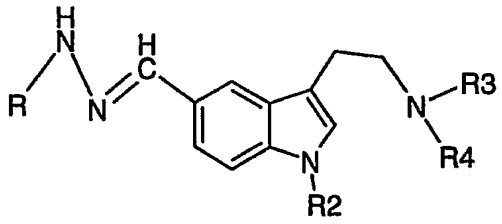
with a hydrazine of the formula [F],

$$R\text{-}NH\text{-}NH_2 \qquad [F]$$

wherein R is hydrogen or acyl, or a salt thereof, under reductive conditions to the compound of the formula [D], or the salt thereof.

9. Process of claim 8, wherein R is hydrogen or lower alkanoyl, and each of R3 and R4 is methyl.

10. A compound of the formula [D]

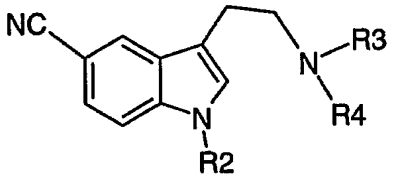


[D]

wherein

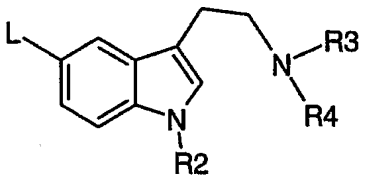
R is hydrogen or acyl, R2 is hydrogen or a protecting group, and each of R3 and R4 is hydrogen or lower alkyl, or a salt thereof.

11. A process for the manufacture of a compound of the formula [E]



[E]

as shown in claim 8, wherein R2 is hydrogen or a protecting group, and each of R3 and R4 is hydrogen or lower alkyl, comprising reacting a compound of the formula [G],

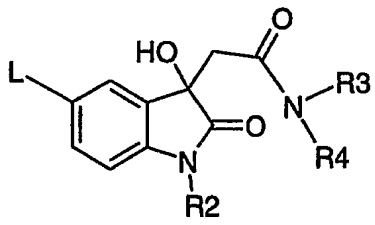


[G]

wherein R2, R3 and R4 are as just defined, or a salt thereof, and L is halogen or, unsubstituted or substituted alkanesulfonyloxy or arylsulfonyloxy, with a cyanide salt, where required, in the presence of a catalyst to the compound of the formula [E] or the salt thereof.

12. A compound of the formula [G] as shown in claim 11, or a salt thereof.

13. A process for the manufacture of a compound of the formula [G] as shown in claim 11, or a salt thereof, comprising reducing a compound of the formula [H],



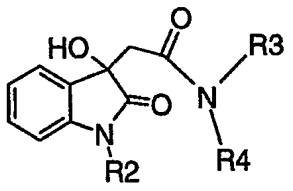
[H]

wherein R2, R3 and R4 and L are R2 is hydrogen or a protecting group, and each of R3 and R4 is hydrogen or lower alkyl, and L is halogen or unsubstituted or substituted alkanesulfonyloxy or arylsulfonyloxy, in the presence of borane, and subjecting the

resulting product(s) to removal of borane from any amino borane intermediates to a subsequent oxidation/de-hydrogenation with an oxidant, in order to yield the compound of the formula [G], or salt thereof.

14. Process of claim 13, wherein the compound of the formula [H] is manufactured

a) either from a compound of the formula [I],

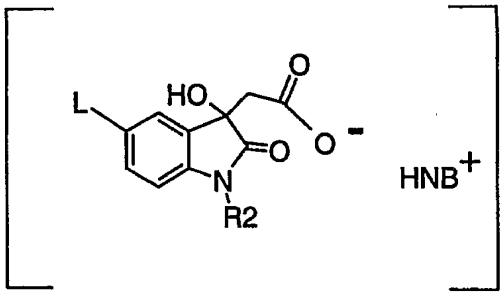


[I]

wherein R2, R3 and R4 are as defined in claim 13, by reacting it with an electrophile capable of introducing a leaving group Lresulting in a corresponding compound of the formula [H],

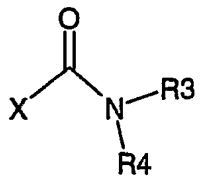
or

b) by reacting a compound of the formula [K*],



[K*]

wherein R2 and L are as defined in claim 13, and NB is a tertiary nitrogen base where the nitrogen is not part of a ring, with a compound of the formula [L]

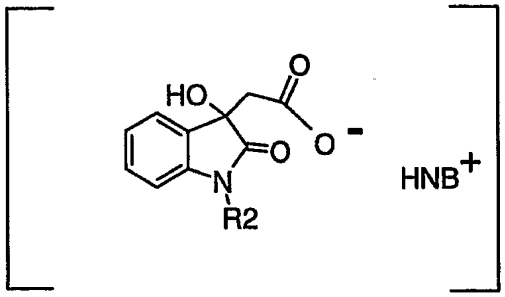


[L]

wherein X is halogen and R3 and R4 are as defined claim 13, to give the compound of the formula [H].

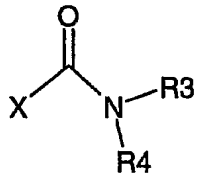
15. Process of claim 14, where in variant a) the electrophile capable of introducing a leaving group L is a halo-succinimide.

16. Process of claim 14, where in variant a) the compound of the formula [K*] is formed by reacting a compound of the formula [K],



[K]

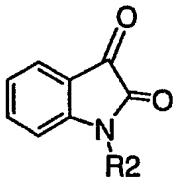
wherein R2 and NB are as defined in claim 14, with a compound of the formula [L],



[L]

wherein X is halogen and R3 and R4 are as defined in claim 14, to give the compound of the formula [K*].

17. Process of claim 16, where the compound of the formula [K] is obtained by reacting an isatine compound of the formula [M],



[M]

wherein R2 is as defined in claim 16, with malonic acid in the presence of a pyridine and in the absence or presence of a N,N-di-(lower alkyl)-lower alkanoylamide, a lower alkanol, or a di-lower alkylsulfoxide, followed by conversion of the resulting compound which is present as a salt of a pyridine into the salt of the base NB given in formula [K].

18. Process of claim 17, wherein the isatine compound of the formula [M] is reacted in the presence of pyridine and/or one or more picolines.

19. Process of claim 17, wherein the isatine compound of the formula [M] is reacted in presence of a N,N-di-(lower alkyl)-lower alkanoylamide, a lower alkanol, or a di-lower alkylsulfoxide.

20. Process of claim 17, wherein the isatine compound of the formula [M] is reacted in presence of methanol, ethanol, dimethylsulfoxide or N,N-dimethyl formamide.

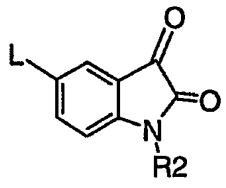
21. Process of claim 17, wherein the isatine compound of the formula [M] is reacted in in the additional presence of an ester as a cosolvent.

22. Process of claim 21, wherein ester cosolvent is selected from lower alkyl alkanoates.

23. Process of claim 17, wherein the reaction of the isatine compound of the formula [M] and the conversion of the product salt of a pyridine into the corresponding salt of the formula [K] take place in the same reaction vessel.

24. Process of claim 17, wherein the reaction of the isatine compound of the formula [M] and the conversion of the product salt of a pyridine into the corresponding salt of the formula [K] and also the reaction of the compound of the formula [K] with a compound of the formula [L] to a compound of the formula [I] take place in the same reaction vessel.

25. Process of claim 14, where in variant b) the compound of the formula [K*] is obtained by reacting an isatine compound of the formula [M*],



[M*]

wherein R2 and L are as defined in claim 14, with malonic acid in the presence of a pyridine and in the absence or presence of a N,N-di-(lower alkyl)-lower alkanoylamide, a lower alkanol, or a di-lower alkylsulfoxide.

26. Process of claim 25, wherein the isatine compound of the formula [M*] is reacted in presence of pyridine and/or one or more picolines.

27. Process of claim 25, wherein the isatine compound of the formula [M*] is reacted in further presence of a N,N-di-(lower alkyl)-lower alkanoylamide, a lower alkanol, or a di-lower alkylsulfoxide.

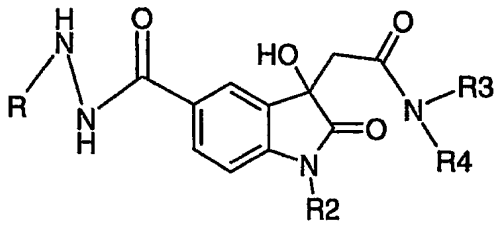
28. Process of claim 27, wherein the isatine compound of the formula [M*] is reacted in presence of methanol, ethanol, dimethylsulfoxide or N,N-dimethyl formamide.

29. Process of claim 25, wherein the isatine compound of the formula [M*] is reacted in in the additional presence of an ester as a cosolvent.

30. Process of claim 29, wherein ester cosolvent is selected from lower alkyl alkanoates.

31. Process of claim 25, where the reaction of the isatine compound of the formula [M*] and the conversion of the product salt of a pyridine into the corresponding salt of the formula [K*] preferably take place in the same reaction vessel.

32. A process for the manufacture of a compound of the formula [B] as shown in claim 1, wherein R is hydrogen, R2 is hydrogen or a protecting group, and each of R3 and R4 is hydrogen or lower alkyl, or a salt thereof, comprising reducing a compound of the formula [C],



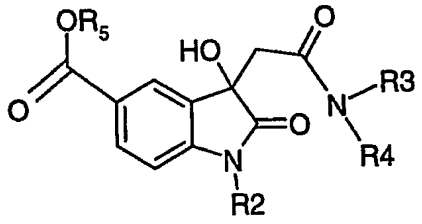
[C]

wherein R is hydrogen, and R2, R3 and R4 are as defined for formula [B] above, or a salt thereof, in the presence of borane, and subjecting the resulting product(s) to removal of borane from any amino borane intermediates and to a subsequent oxidation/de-hydrogenation with an oxidant, thus producing a compound of the formula [B], or a salt thereof.

33. A compound of the formula [C] as shown in claim 32, or a salt thereof.

34. A compound of the formula [C] according to claim 33, wherein each of R3 and R4 is methyl.

35. A process for the manufacture of a compound of the formula [C] as shown in claim 32, or a salt thereof, wherein R is hydrogen or acyl, R2 is hydrogen or a protecting group, and each of R3 and R4 is hydrogen or lower alkyl, or a salt thereof, comprising reacting a compound of the formula [N],



[N]

wherein R2, R3 and R4 are as defined for formula [C] and R_5 is unsubstituted or substituted alkyl, with a hydrazine of the formula [F]

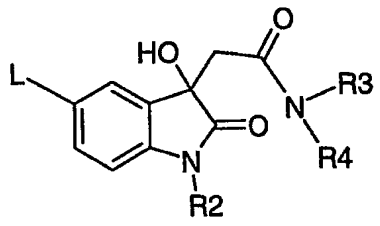
$$R\text{-}NH\text{-}NH_2 \qquad [F]$$

wherein R is as defined for formula [C], or a salt thereof,

to a compound of the formula [C].

36. Process of claim 35, wherein R_5 in formula [N] is lower alkyl, and/or R in formula [F] is hydrogen.

37. A process for the manufacture of a compound of the formula [N] as shown in claim 35, wherein R2, R3 and R4 are as defined in claim 35, comprising reacting a compound of the formula [H]



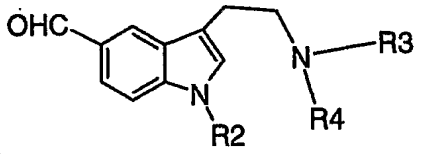
[H]

wherein R2, R3 and R4 are as defined in claim 35, and L is halogen, unsubstituted or substituted alkanesulfonyloxy or arylsulfonyloxy,

with carbon monoxide in the presence of the corresponding alcohol R_5-OH in the presence of a catalyst and a tertiary nitrogen base, to the compound of the formula [N].

38. Process according to claim 37, where preferably the compound of the formula [H] is obtained as described in claim 14.

39. A process for the manufacture of a compound of the formula [B] as shown in claim 1, or a salt thereof, comprising reacting an aldehyde of the formula [O],

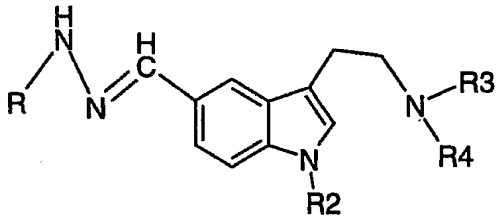


[O]

, or a salt thereof, with a hydrazine [F]

$R\text{-}NH\text{-}NH_2$ [F]

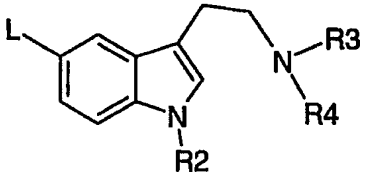
and then subsequent reduction of the resulting hydrazone of the formula [D]



[D]

, or salt thereof, with the hydrazine of the formula [F], or salt thereof, to a compound of the formula [B], or a salt thereof; wherein each of R, R2, R3 and R4 in the compounds mentioned is as defined in any one of claims 1 or preferably 2 and L is halogen.

40. Process according to claim 39, where the compound of the formula [O] given above, or salt thereof, is obtained from a compound of the formula [G]



[G]

wherein each of R, R2, R3 and R4 is as defined in claim 39, or a salt thereof,

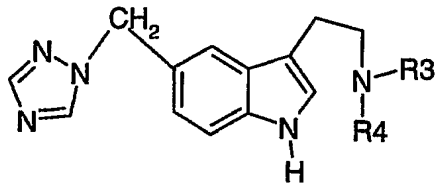
by reacting it with first a lithium alkyl compound to form the lithio derivative and then with DMF or triethyl formate, to obtain a corresponding compound of the formula [O], or a salt thereof after hydrolysis.

41. A compound of the formula [B] as shown in claim 1, or a salt thereof.

Abstract

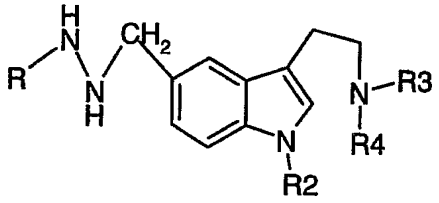
Synthesis Methods and Intermediates for the Manufacture of Rizatriptan

The invention relates to a process for the manufacture of an 1,2,4-triazol-1-yl compound of the formula [A],



[A]

or a salt thereof, wherein each of R3 and R4 is hydrogen or lower alkyl, said process comprising reacting a hydrazine compound of the formula [B]



[B]

wherein R is hydrogen or acyl, R2 is hydrogen or a protecting group, and R3 and R4 have the meanings as defined above for compounds of the formula [A], or a salt thereof with a 1,2,4-triazolyl forming reagent,
if R is acyl in formula [B], removing an acyl group R before the reaction of the compound of the formula [B] with the 1,2,4-triazolyl forming reagent,
and removing any protecting group R2 to produce the compound of the formula [A], or a salt thereof, and, if desired, converting a salt of a resulting compound of the formula [A] into a free form of a compound of the formula [A], converting a resulting free form of a compound of the formula [A] into a salt or converting a salt of a compound of the formula [A] into a different salt. In addition, novel intermediates and methods for their synthesis are presented. This allows for the synthesis of the anti-migraine agent Rizatriptan.